ANNUAL REPORT
OF
PROGRAM ACTIVITIES
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES
FISCAL YEAR 1979

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service - National Institutes of Health

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HIGHLIGHTS

Of 23,805 competing grant applications received, 17,364 were assigned for review to DRG.

Four new study sections were chartered: Biochemical Endocrinology; Chemical Pathology; Diagnostic Radiology and Nuclear Medicine; and Mammalian Genetics.

Phase II of the Report to the Director, NIH, by the Grants Peer Review Study Team was published. Over 3,000 copies were mailed out to those who participated in the opinion poll.

The instructions for completing the PHS 398 research grant application form were revised and mailed out to grantee institutions on demand.

The NRSA payback agreement and assurance forms were revised following legislative changes to the program, the extension of which was signed into law on November 9, 1978.

The Trainee Appointment File was redesigned to contain trainee appointment records for several years making more information available on indirect trainees supported under PHS training grants.

The acquisition and installation of word processing equipment and establishment of a prototype service unit capable of handling the typing needs of about 20 study sections is intended to substantially reduce the clerical workload and overtime of the study sections.

Extramural program statistics for fiscal years 1968-78 were compiled and analyzed and a set of 35 mm slides illustrating trends was developed and presented to the Director, NIH, and selected audiences.

An NIH Review Scientist Registry and Consultant File was officially initiated.

OFFICE OF THE DIRECTOR

Dr. Carl D. Douglass, Director, DRG, attended meetings of the Editorial Advisory Committee for "American Men and Women of Science" and the Policy Advisory Group, Competitive Research Grants Office, USDA, during December and participated in a grants symposium held at the University of Maine, Orono, Maine, October 11-12, and the annual meeting of the Western Association of Graduate Schools in Colorado Springs, Colorado, March 4-6.

Dr. S. Stephen Schiaffino, Deputy Director, DRG, attended a grants symposium at the University of Maine, Orono, Maine, on October 11; addressed the Third Clinical Congress, American Society for Parenteral and Enteral Nutrition, Inc., in Boston, Massachusetts, on February 2; participated in a NIH conference on grants and contracts held at the University of Michigan, Ann Arbor, Michigan, on March 12, and in a public affairs symposium at a meeting of FASEB in Dallas, Texas, on April 3. On May 9, Dr. Schiaffino addressed a meeting of the Society of Chairmen of the Academic Radiology Departments in Rochester, New York, and attended the third annual meeting of the National Academy of Clinical Biochemistry in New Orleans, Louisiana, on July 14.

Dr. Schiaffino was named to two new committees during this reporting period: the Senior Executive Service Committee and the Research Resources Coordinating Committee. He continued to serve as chairman of the NIH Forms Committee and as a member of the Executive Committee for Extramural Affairs; ECEA Subcommittee on Research; NIH Task Force on Travel; Executive Secretaries Review Activities Committee; Advisory Group on Diagnostic Radiology; Long Range Planning Group on NIH Facilities; Coordinating Committee for NIH Minority and Women Research and Training; and the Implementing Committee for the Grants Peer Review Study Team.

Dr. Samuel Schwartz, Associate Director for Scientific Review, is chairman of the NIH Committee to develop procedures for amendments and rebuttal letters, and has served this year as chairman of the Selection Review Board for the Extramural Associates Program. He is co-chairman of the Executive Secretaries Review Activities Committee (ESRAC), and of the committee to implement GPRST Recommendation No. 38. He is a member of the NIH Advisory Committee on Public Advisory Group Membership; the NIH Committee on Selection Procedures: the NIH training design team, and the Grants Associates Board.

DRG staff contributed substantially to the preparation and distribution of Phase II of the Report to the Director, NIH, by the Grants Peer Review Study Team (GPRST) which was published in July. The report contains opinions on the NIH grants peer review system drawn from public hearings, letters, and a survey of 1975-76 review groups. Copies were mailed to all current members of the initial review groups, advisory councils and boards, NIH staff, hearing witnesses, and letter respondents.

To implement an approved recommendation of the GPRST, notices were published in the NIH Guide for Grants and Contracts, the Federal Register, and

scientific journals, soliciting nominations for membership on the NIH initial review groups, advisory councils and boards.

A committee to review procedures for selecting members of the initial review groups was established during fiscal year 1979.

Information and Instructions (I & I) Memorandum OD 79-3 was prepared and distributed to NIH staff describing in detail the procedures to be followed for solicitation and nomination for membership on initial review groups, and a similar memorandum is being prepared for membership on advisory councils and boards.

An NIH Review Scientist Registry and Consultant File was officially initiated and many thousand names submitted including, where identifiable, women and minority scientists. The many problems associated with the development of the registry are receiving careful study so that a smooth well-functioning operation will be conducted.

The 4500 series of Manual Issuances, which deal with peer review policy and procedures, was thoroughly revised and updated to include approved GPRST recommendations. Final drafts of the Manual Issuances were forwarded to the Policy and Procedures Office, OD/NIH in May, and await approval before preparation in final form for distribution to NIH staff.

The Priority Score Committee, charged to study BID practices regarding the use of "raw" and "normalized" priority scores, completed its assignment and forwarded its report and recommendations to the Chairman, Implementation Committee, in February.

Revised instructions for completion of research grant application form PHS 398 were published in the NIH Guide for Grants and Contracts (Vol. 8, No. 10, July 23, 1979) and, effective that date, have been included in the research grant application kits and mailed on demand to grantee institutions.

The Executive Secretaries Review Activities Committee (ESRAC) began planning workshops for executive secretaries on conflict of interest.

The Orientation Committee prepared drafts of orientation handbooks for members of initial review groups, grants assistants, and for advisory councils and boards. Plans are also being formulated for the orientation meetings.

OD staff made substantial contributions to the preparation of Information and Instructions Memoranda (I & I) on conflict of interest, and to the I & I Revision Committee on amendments and rebuttals. Staff also provided significant input to the work of the STEP Committee (Staff Training on Extramural Programs), and continued to prepare the periodic listings of NIH Conferences.

The Division's formal employee training program continued throughout the year to meet the career development needs of the staff. Many employees were able to maintain their continuing education efforts under the Upward Mobility Program by attending classes at the University of the District of Columbia. In addition, under the provisions of the Government Employees Training Act,

234 employees enrolled in training courses designed to enhance their job performance.

The Personnel Office continued to provide new employees an opportunity to attend the DRG Orientation Program and worked closely with the Employee Advisory Committee on providing training programs of current interest to employees. An example of the cooperative effort was the presentation of the cardiopulmonary resuscitation course which was made available to all DRG employees.

The EEO Counselor participated throughout the year in the ongoing activities of the EEO program. In March, he chaired the program committee that planned the regularly scheduled quarterly meeting of the Council with the Director, NIH, and at the same meeting, presented a paper on NIH counseling services. The Counselor served as acting chairman of the Council and Executive Board August 20-24, and as chairman of the Standing Committee on Counseling; Counseling Experiences Forum; the special Executive Board Committee on Council Operation, the annual DEO/EEOC Orientation Seminar for newly appointed counselors, and the Affirmative Action Plan Committee to develop the DRG 1979-1981 Affirmative Action Plan.

The Counselor was a member of the Council Executive Board, the EEO Council Planning Committee for the Annual Program Review Seminar held at Harpers Ferry, W. VA in July; the EEO Council Recommendations Coordinating Committee, the DRG Employee Advisory Committee, and an ad hoc member of the Council Organizing Committee. He also represented the Division for input/output of NIH/EEO data and related information.

The Counselor also participated in DRG employee orientation activities by providing new employees with information about the EEO program, attended regular and special meetings of the NIH EEOAC, NIH EEOAC/Executive Board, the DRG Employee Advisory Committee, and special minority program activities such as Black Week, Asian-American Week, Hispanic Week, and Dr. Martin Luther King, Jr. Program.

The Employee Advisory Committee (EAC) continued to serve in an advisory capacity to the Director and provide a channel through which a multiplicity of concerns were conveyed to the Division's top management for resolution. In November the Committee conducted a poll through "Continuing to Keep you In Informed" for the purpose of changing the name of the "Top Box." The box, now called the "Voice Box", is located on the 3rd floor of the Westwood Building across from the main elevators. The Committee encourages its use as a means whereby the views of staff can be heard.

The NIH Women's Advisory Committee (WAC), formed in 1976 with delegates from each BID, has the responsibility to represent all NIH women. It has a working charter and a mandate to advise the Federal Women's Program Coordinator (FWPC); to serve as an advocate group for women, and a communication channel between women and management; and to identify problems and recommend solutions.

Of particular note this year was the formation of the By-Laws for the

WAC, and the approval by the Division of Personnel Management of the Collateral Duty Position Description for the NIH Women's Advisory Committee members.

During the year, the WAC sponsored several seminars, including one on the Universal Social Security Plan, and one on the Total Compensation Comparability Plan.

The WAC sponsored the videotape "Alice in FES Land," which is shown throughout NIH. The videotape is considered to be a valuable tool in preparing for a desk audit under the new Federal Evaluation System (FES).

EXTRAMURAL ASSOCIATES PROGRAM

The Extramural Associates Program is a special adaptation of the opportunities available under the Intergovernmental Personnel Act (IPA) to promote most effectively, the entry and participation of ethnic minorities and women in NIH supported research. Under the program, the NIH invites key administrators involved in science, from schools that contribute significantly to the pool of minorities and women in science, to spend 6 months in residence in Bethesda, MD. Salary, travel, and related expenses, along with a special per diem to offset the cost of living in the Washington area, are reimbursed by the NIH to the limit allowed under the IPA.

The Program was initiated with 13 participants in this, its first year. Five of the Associates came on board for the term of August 1, 1978 to January 31, 1979. They were:

Dr. William J. Hamm, Professor and former Chairman of the Department of Physics, St. Mary's University, San Antonio, Texas

Dr. John T. Hayes, Professor and former Chairman of the Division of Natural Sciences and Mathematics, Paine College, Augusta, Georgia

Dr. Jean L. J. Lum, Professor and Chairman of the Department of Professional Nursing, University of Hawaii, Monoa, Honolulu, Hawaii

Dr. Marian L. Wilson, Associate Professor of Biology, and Assistant to the Vice President for Research and Development, Chicago State University, Chicago, Illinois

Dr. Bonnie G. Wood, Assistant Professor of Zoology, and Director of Medical Technology, University of Maine, Orono, Maine

The second group of Associates, of which there were eight, came on board for the second term, February 1, 1979 to July 31, 1979. They were:

Dr. James B. Abram, Professor of Biology, Hampton Institute, Hampton, Virginia

Dr. Fred A. Christian, Professor of Zoology, and Director of the Health Research Center, Southern University, Baton Rouge, Louisiana

Dr. William B. Harrell, Professor and Chairman, Department of Medicinal Chemistry, Texas Southern University, Houston, Texas

Dr. Edward G. High, Professor and Chairman, Department of Biochemistry and Nutrition, Meharry Medical College, Nashville, Tennessee

Dr. Marion Mann, Dean of the Medical School, Howard University, Washington, D.C.

Dr. Elizabeth J. Rock, Professor, and Director of the Office of Sponsored Research Wellesley College, Wellesley, Massachusetts

Dr. Julian E. Thomas, Professor of Biology, Tuskegee Institute, Tuskegee, Alabama

Dr. Arthur C. Washington, Professor of Biology, Director, Biochemistry Research Lab, Prairie View A&M University, Prairie View, Texas

While on detail at the NIH, the Associates had various assignments. Some of these included: the initial review system, a council meeting, the Division of Research Resources, a site visit, and approximately 3 weeks to 1 month working as a member of the program staff of an appropriate B/I/D. The balance of time spent here was with agencies outside the NIH, such as NSF, ADAMHA, HRA and HSA.

The Associates worked closely with an Advisor chosen with their special talents and interests in mind, who advised them on contact people, and who also acted as a guide during the first weeks the Associates were here.

Applications for the Program are accepted once a year, with the next receipt date projected to be January 31, 1980. Applications are reviewed competitively by a panel modeled on the study sections. Selected applications for the 1980-1981 academic year will be announced by Dr. Thomas E. Malone by April 30, 1980.

During the year under review, the Grants Associates Program included 16 Grants Associates: 6 women (37.5 percent) and 2 minorities (12.5 percent). Four (25 percent) came from the NIH intramural area and four from other Federal agencies.

The GA Program will have graduated 9 of these 16 Grants Associates at the end of the fiscal year (8 have already graduated and all but one taking positions at NIH: NIAMDD--3, and one each in NICHHD, NINCDS, NEI, OD/NIH, and one with NIDA, ADAMHA). With the inclusion of these 9 graduates, the total of GA graduates since the first class in 1963 will be 131: 115 males (88 percent), 16 females (12 percent), and 16 minorities (12 percent). This is an increase of 1 percent each of women and minorities over last year.

The number of possible Grants Associates this year was reduced because of the Federal hiring freeze at the beginning of the fiscal year. Therefore, there was a hiatus of 6 months (from December to May) during which no GAs were entered on duty.

The Grants Associates Board welcomed its new chairman this year, Dr. George Galasso, Chief, Development and Applications Branch, MIDP, NIAID, and a new Vice Chairman, Dr. Suzanne Stimler, Director, Biotechnology Resources Program Branch, DRR. This year it was recommended and approved that Board memberships be on a fiscal rather than a calendar year basis to be consistent with the various annual reports that are due each fiscal year. Hence, the next new Board members will be appointed in October 1979. Terms will remain the same, but the current and next two chairmen will have their terms extended slightly for the sake of continuity.

The Board initiated a Committee on Preceptor Role resulting in a report identifying those areas of responsibility common to all preceptors. It is understood that the mechanics and style of fulfilling these responsibilities remain an individualized one between preceptor and GA. This document, available in the GA Handbook, also serves new preceptors well in their orientation to the role.

In addition to continued affirmative action recruitment, a GA Program announcement was placed in the NIH Guide for Grants and Contracts on April 13, 1979; during the first 3 weeks after issue, 126 inquiries were received and there have been daily inquiries from across the country. This year the first Directory of Former Grants Associates (up to FY 1978) was published. This was distributed to each current and former Grants Associate and GA Board members. The Directory is included with the GA Program announcement as further publicity for the Program. It is also included in application kits. Several positive unsolited comments were received. The Directory will be updated annually.

The amount of formal training for Grants Associates (courses and seminars) generally has been quoted as consuming approximately 25 percent of the Grants Associates year. In fact, it is less than that. Last year it was only 16 percent of the GA year; this year, only 15 percent. Twelve GAs took 15 different

courses, an average of 3.75 courses per GA, for a combined total of 1,482 hours of course work (an average of 123.5 hours per GA or 6 percent of GA year). The Seminar Series included 39 seminars ranging from 2 to 8 hours, totalling 170 hours or 8 percent of the GA year. The total cost of the formal training was $7,357 ($5,342 in tuition and $2,015 in travel, which includes travel for the Regional Office seminar). The Seminar Series included 20 non-GAs who were selected for seminar participation, including two from DRG. The Series still proves to be a valuable training experience for the non-GA.

The Office has had to operate with a depleted staff complement since April, while the workload has remained at a high level.

Telephone and written inquiries on NIH research and training support mechanisms, research programs, and requests for data on NIH-supported research that entailed manual or computer runs on different research areas or disease entities remained at about the same level as in previous years. About 30 congressional inquiries, other than those for publications, were responded to by letter or telephone. A number of press releases on availability of publications and senior staff appointments were prepared during the year.

The Office spearheaded the distribution of over 3,000 copies of Phase II of the Report to the Director, NIH, by the Grants Peer Review Study Team, and mailed out several thousand copies of the revised instructions to the research grant application form (PHS 398) to grantee institutions in response to their requests.

A revised return address label was initiated and designed for all application forms to facilitate hand delivery of completed applications to the Westwood Building by commercial carriers. The Office also revised and clarified the schedule of receipt dates to eliminate telephone inquiries from potential applicants confused by footnotes to the schedule originally published.

The staff revised the pamphlet, National Institutes of Health Grants and Awards, and updated publications such as the Scientific Directory and Annual Bibliography, the NIH Almanac, and documents submitted by non-Federal organizations and the Library of Congress.

There continued to be a steady demand for documents disseminated by the Office: NIH Advisory Groups, Basic Data Relating to the National Institutes of Health, NIH Guide for Grants and Contracts, listings of new grants and awards, and articles on the review process the most frequently requested. There was a constant demand for a publication describing the NIH programs and support mechanisms and the lack of such a publication continued to create problems.

In conjunction with the NHLBI grants management staff, viewings of the DRG slide series, How a Research Grant is Made, were arranged for visitors from grantee institutions. The slide series was also shown on request to new staff members and scientists from the I/Ds.

An average of 12 individuals a week from the scientific community and the general public visited the Office for information, application kits, and publications. Several were briefed on the organization and functions of the Office, of DRG and NIH generally; on the support mechanisms; the review process, and available publications.

The Acting Chief serves as the Division's Freedom of Information Coordinator and Acting Privacy Act Coordinator. During the year under review, only 11

requests for information actually cited the FOI Act. Requests under the Privacy Act declined when, beginning in the fall of 1978, summaries of initial review group evaluations were required to be sent automatically to each grant applicant, but requests have begun to come in for names of primary and secondary reviewers and for copies of their actual comments. OGI, in conjunction with SRB, will be exploring the best way to handle such requests.

The Acting Chief continues to represent the Division on the NIH Task Force to Implement Regulations on Nondiscrimination on the Basis of Handicap.

Seminars on Human Interaction in the Work Environment, and Executive Planning and Management were attended by the Acting Chief. Members of the supporting staff took courses in communicative skills and language arts, English composition, and shorthand.

During the year under review, the Office of Management and Budget approved two NIH National Research Service Award application forms: Institutional Grant (PHS 6025) and the Individual Award (PHS 416). The Office of Research Manpower (ORM), with a staff of two, provided the administrative back-up to both drafting committees, handled the OMB clearance process, and arranged for the forms to be printed. One staffer served on both drafting committees. In addition to the training forms, ORM spearheaded the revision of the Statement of Appointment of Trainee Form, developed a draft of the Final Invention Statement, and a draft instruction sheet for the noncompeting continuation Research Career Development Award, and worked on the draft instructions for the competing Research Career Development Award application. The latter two drafts were based on the use of the revised PHS 398 and PHS 2590 application forms.

The legislative extension of the NRSA program, signed into law November 9, 1978, mandated a number of changes in the program, especially related to payback. In implementing the changes, ORM revised the payback agreement and assurance forms, developed an addendum to the basic policy document, a position paper on the effective date of the legislative changes, and a draft NIH Guide release. During the year, other position papers were also developed on monetary payback and the infamous 25/75 ratio of institutional expenses to trainee costs on training grants.

ORM, working with the Statistics and Analysis Branch, provided the statistics needed by the National Academy of Sciences for their Report on Personnel Needs and Training for Biomedical and Behavioral Research. Even though legislation changed the requirement from an annual report to once every 2 years, statistics will be provided on an annual basis for purposes of an off-year report and to spread out the workload. Other statistics provided by ORM included the Black College Survey for the Federal Interagency Committee on Education and individual awards and applications involving foreign sponsors for the Canadian Medical Research Council. ORM is working toward a basic set of training program statistics that will provide information quickly to many sources.

ORM responded to many inquiries, from the field and within the Government, on the training programs and their application forms. ORM over the years has developed the reputation of being the Office to handle inquiries involving student support.

The program analyst, ORM, served as a co-leader on one of the modules at the GMAC Workshop at Airlie House in March. This most successful module resulted in a report on payback problems and their solutions.

With much of the forms development completed, increased emphasis on basic training program statistics and improved program management procedures both internally and externally are expected in FY 1980.

The Administrative Branch continued to provide the Division with administrative and financial management (including budget and scientific evaluation grants), property and supply control, space planning and assignment; to maintain supplies of publications and application forms used in the PHS extramural programs; and to be responsible for the efficient running of the components for effective coordination of procedures and services, and to maintain procedures for centralized distribution of application forms by the grantee institutions. A number of studies were conducted and/or directed by the Branch involving several management activities, the results of which may mean a reorganization or the application of new technology within the Division.

Financial Management Section: The Section assisted in administering about $14.8 million for the Division's operations, of which $13.1 million was from the NIH Management Fund, supplemented by $1.7 million from the institutes for the support of the Scientific Review and Evaluation Grants (SREG) awarded to study section chairmen. The Section monitored the expenditures from these through a computer data base system that also provides NIH management with up-to-date monthly cost analyses progress reports. Consultant costs were again paid almost entirely from the SREG's with consequent savings in both time and effort. The Section continues to report approximately 6,500 individual payments made to about 2,500 consultants who submitted 5,800 vouchers to the NIH-wide computer-based system for reporting consultants' incomes. In addition to the audit of the 5,800 consultants' vouchers, about 900 vouchers were audited by this Section for Division employees and others.

The Section prepared the Preliminary Estimate to HEW, the OMB Submission, and the Zero Base Submission for the FY 1980 President's Budget in addition to furnishing information for the FY 1979 Mid-Year Review. Work has been started on the FY 1981 Forward Plan. The Section continues to monitor the orderly flow of obligations and other aspects of budget execution as well as responding to requests from the Division of Financial Management.

Office Services Section: The Section continued to review and approve requests for supplies and equipment needed by the Division; to provide property and supply control; to participate in space planning and assignment; to maintain the Division's mail room; to be responsible for wide distribution of PHS and NIH extramural forms and publications; to maintain liaison with other NIH service components for effective coordination of procedures and services; and the responsibility of maintaining the institutional application control.

The number of grant application kits assembled and handled continued to average around 10,000 a month, and about 9,500 miscellaneous packages were mailed each month. The Mail Unit received and processed approximately 35,000 grant applications of all types, and a large volume of supporting documents, letters, and publications.

Extensive technical contributions were made by staff in the development

of several new and revised forms, including the new PHS 398 (research grant application form).

The Reference Room has been relocated, reduced in size, and some of its material has been decentralized, but its basic function remains intact with the provision of appropriate medical reference texts, and searches for specific scientific publications and material.

REFERRAL BRANCH

The number of applications assigned or processed by the Referral Branch in Fiscal Year 1979 increased from the previous fiscal year by 3 percent. Although competing applications declined from 24,676 to 23,805 (-4 percent), noncompeting applications increased from 13,796 to 15,817 (+15 percent). The percentage of competing applications assigned to NIH rather than to other PHS agencies continues to be approximately 84 percent.

During Fiscal Year 1979, the Branch responded to the receipt of applications resulting from 90 announcements to the scientific community reflecting special emphasis programs of the awarding units, compared with 42 the previous year.

The staff participated in a number of activities during the year under review:

The Branch Chief, Dr. Henry G. Roscoe, participated in a workshop on Extramural Programs for the Pharmacology Research Associates of NIGMS in May. He also participated in the "Introduction to Supervision" course held on the NIH campus in June.

The Assistant Chief for Research, Mr. Frederick Gutter, who retired in June, presented a paper at the annual meeting of the Society for Neurosciences in St. Louis, MO in November.

The new Assistant Chief for Research (temporary title), Dr. Julius Currie, attended a planning workshop for the STEP committee in June.

Mrs. Mildred J. Waters, Project Control, attended a workshop on "Alternative Management Approaches for the 80's" in May, and Mrs. Louise Berkovich, Project Control, attended a course entitled "Time Management for Supervisors" in July.

Several improvements were made in Branch procedures during the year: All 901 requests (ROTs) are now routed through one person who eliminates any duplicate requests. If questions arise, they are referred to the Chief and two Assistant Chiefs.

A new format for recording the number of applications assigned to the study sections is being used. Features of the new format include: (1) separate counts for fellowships and research grant applications; (2) continual updating of study section load because of changes in assignment subsequent to initial assignment; and (3) separate sections for each section chief.

Various groups of executive secretaries, referral officers, and the section chiefs have held meetings in an ongoing effort to rewrite the different study section guidelines. The emphasis is on more clearly written, definitive documents and a consistent format.

For competing applications, page counting has been eliminated in the Receipt and Control Unit. This has allowed the applications to move to the referral officers in a more timely fashion.

The procedure for processing noncompeting supplements has been streamlined. Now only the face page of these applications is required, and institute staff can make budget changes directly on the face page with a pen. An itemized budget is no longer needed. This streamlined procedure appears to be working well for Project Control, SAB, and the awarding BIDs.

Improvements have been made in the processing of continuation applications (type 5). Color coded folders, elimination of unnecessary processing steps, and the use of a bursting machine to separate computer-run pages have improved the efficiency of processing these forms.

Five 3-M microfishe units were replaced with new Bell and Howell units. The old units were constantly breaking down and causing a delay in the initial processing of competing and noncompeting grant applications. This situation should be corrected with the acquisition of the new equipment.

Because of space limitations, copies of grant applications will no longer be retained by Project Control beyond the next receipt date.

APPLICATIONS PROCESSED BY REFERRAL BRANCH FOR FY 1979 COUNCILS

Council		Aug/Oct 1978	January 1979	May 1979	Total FY'79
		COMPETING			
Number of Applications (1)	New	5772	5076	7659	18507
	Renewal	1125	1713	1971	4809
	Supplement	171	121	197	489
	TOTAL	7068	6910	9827	23805
Distribution (percent)	NIH	83.5	85.5	78.9	
	ADAMHA	13.7	11.9	17.9	
	Other (2)	2.8	2.6	3.0	
		NONCOMPETING			
Type 5		3728	4250	6806	14784
Interim		216	415	402	1033
(Administrative)	TOTAL	3944	4665	7208	15817
COMPETING		7068	6910	9827	23805
NONCOMPETING		3944	4665	7208	15817
	GRAND TOTAL	11012	11575	17035	39622

(1) Includes applications for regular research, program projects, centers, construction, training, fellowships, career awards, and minority programs.

(2) Includes FDA, HRA, OH

The Research Analysis and Evaluation Branch continued to be concerned with providing staff resources to the Office of the Director, NIH, OD-DRG, other NIH directorates and program officials in the analysis, evaluation, development and planning efforts in the extramural biomedical research programs. The Branch prepared studies on virology research, immunology, marine mammal research, clinical biochemistry, health services research, epidemiology, pain research, traditional chemistry research (other than biochemistry), and various studies relating to principal investigators on NIH research grants.

RAEB is responsible for producing the NIH Annual Inventory of Clinical Trials through contacts with various institutes. The NIH Inventory of Clinical Trials is a central repository of information on the hypotheses being tested, fiscal and administrative data, population characteristics of patients, experimental design data, and bibliographic data on clinical trials supported by NIH. The Inventory has also begun to be used as a resource base for a variety of other purposes including the specific manner that clinical trials fit into the total pattern of NIH responsibilities in biomedical research and development.

The staff undertook the following studies: An analysis of key research events that made possible a recent practical advance in the biomedical sciences; analysis of funding of all competing research and training applications by sex of principal investigators; support of new principal investigators by NIH: 1968-1978; new methods for estimating funding in various extramural program areas; analyses delineating trend of declining M.D. researchers' participation in investigator-initiated NIH research projects; new applicants for NIH research grants, their increasing numbers and estimate of their chances of success; the length of research grant applications as a workload factor in scientific merit reviews; the use of the priority score scale by selected IRGs; characteristics of a cohort of new principal investigators; and characteristics of research leaders on sub-projects of large grants.

The staff served as members or participated in the operation of the following committees; Grants Associates Board, Extramural Associates Review Panel, DHEW committee to coordinate toxicology and related programs, Nutrition Coordinating Committee, Technical Review Committee for National Research Council contract proposal, IMPAC Evaluation Sub-Committee on Technical Data, NIH Clinical Trials Committee, Office for Medical Applications of Research, Federal Interagency Chemistry Representatives, HEW Steering Committee for Development of Health Research Principles (NIH staff member); NIH OPPE Officers Meeting (regular standing committee established in FY 1979); and various SATT work groups.

RAEB continues to be involved in a number of resources development activities as bases for studies contributing to the evaluation of NIH science base activities. Among the resources being developed are: a longitudinal file of all applications and awards to individual investigators; a methodology for delineating the science base by whether projects are primarily focused on

disease and disease processes or on more fundamental processes, and by arraying such a description with other determinants such as extent of human subjects participation in the research or extent to which the research activity is targeted by the institutes; development for more consistent sets of terms for characterizing NIH supported research activities by parameters such as scientific discipline, disease, research material, experimental tools and techniques, names of substances, and so on. Other resources development activities within the Branch include contributions to the design and establishment of a variety of specialized data bases requested by NIH-OD and some of the B/I/Ds.

The Branch worked closely with the NIH Office of Program Planning and Evaluation to prepare charts, text, and other materials for an overview of research and development activities in terms of science base, clinical applications, technology transfer, and research training (SATT). The NIH Director used these analyses of institute programs by SATT and mechanism of support in his Research Plan review sessions with each of the institutes, and the NIH composite of SATT at congressional hearings. The relationship between SATT and specific kinds of activities in the R&D spectrum supported by the Public Health Service was described in broadened definitions for use of all the DHEW health agencies. The definitions were developed in cooperation between RAEB, the Division of Resources Analysis, and representatives from CDC and OASH. A "SATT primer", in which RAEB contributed a substantial part of the definitions and illustrative text, was prepared for the use of the Director's Advisory Committee.

Applications assigned to the Scientific Review Branch for review for scientific merit during Fiscal Year 1979 totaled 17,364. In response to the heavy workload, four new study sections were chartered during the year: the Biochemical Endocrinology Study Section, the Chemical Pathology Study Section, the Diagnostic Radiology and Nuclear Medicine Study Section, and the Mammalian Genetics Study Section.

The heavy workload problems, which are continuing into Fiscal Year 1980, have been exacerbated by inadequate space, outmoded equipment, and insufficient personnel. Several studies will be undertaken during the next fiscal year to improve operating procedures and so alleviate the situation. Nonetheless, additional space and additional personnel remain essential components for an improved peer review system.

Workshops or Symposiums Sponsored by Study Sections

The Allergy and Immunology Study Section sponsored a workshop in Bethesda, MD, on October 31 and November 1, on Cell Hybridization in Immunology. The workshop, co-chaired by Drs. J. Donald Capra and Norman R. Klinman, had 15 speakers, including 4 from Europe, and 82 participants. The history, development, present usefulness, and potential uses of hybridomas in the field of immunology were discussed. Included were the applications to study B cells and B cell subpopulations and also to probe antibody structure, antibody diversity, and cellular antigens. The latter topic included both major histocompatibility related antigens and antigens of transformed cells. The conference members concluded that the technology of hybridization of antibody producing cells with continuous plasma cell lines to yield hybridomas which secrete monoclonal antibodies in large amounts is an important development, which has major implications for immunology at the diagnostic, therapeutic, and fundamental levels.

The Hematology Study Section, the Division of Blood Diseases and Resources, NHLBI, and the Blood Program, NIAMDD, sponsored a symposium in San Francisco, CA, June 15-17 on "Aplastic Anemia: A Stem Cell Disease." There were approximately 100 participants. The objective of this conference was to discuss several rapidly expanding areas of research in the field of aplastic anemia, including the clinical aspects of aplastic anemia, colony growth in vitro, cellular and humoral effects in marrow function, and other possible mechanisms of stem cell dysfunction leading to aplastic anemia. The following specific recommendations were made: (1) studies of stem cell growth systems in both short- and long-term cultures are of high priority; (2) biologically active factors in marrow culture should be purified and characterized in chemical and antigenic terms; (3) the interaction between target cells and myelotoxic agents should be examined at the molecular level; (4) the basis for genetic predisposition for marrow damage should be sought in susceptible animals and humans; and (5) aplastic anemia is most effectively treated by marrow transplant in those individuals in which this procedure is feasible. The proceedings of this conference will be published and disseminated to the scientific community. It is anticipated

that this publication will help to define the stem cells of the hemopoietic tissue, to determine the important features in their proliferation, and to discover the causes of disorders in their development. Information about the behavior of these primitive cells should lead to a better understanding and management not only of aplastic anemia but also of other forms of marrow failure, including leukemia.

With the cooperation of the Primate Research Centers Advisory Committee and the Oregon Regional Primate Research Center, the Nutrition Study Section sponsored a workshop on Nonhuman Primate Nutrition and Nutritional Modeling at the Center in Beaverton, Oregon on October 23-24. The first day was spent reviewing nonhuman primate nutritional requirements. Six invited speakers reviewed information currently available for all nutrients, with special emphasis on diet formulation, protein requirements, and nutritional requirements during breeding and pregnancy. The second day was spent reviewing primate models currently utilized in nutritional research, including bile acid metabolism and gallstones, infectious disease, malnutrition and mental development, alcoholism, and diabetes. The proceedings are to be published.

In March, the Toxicology Study Section sponsored a symposium entitled "Aquatic Toxicology." The Chairman, Dr. Marion Anders of the University of Minnesota, introduced the speakers and served as panel discussion director following the formal presentations. The following individuals spoke on selected topics: Dr. John L. Laseter, University of New Orleans, "Contamination of the Aquatic Environment"; Dr. John J. Lech, Medical College of Wisconsin, "Metabolism and Disposition of Xenobiotics in Fish"; Dr.Foster L. Mayer, U.S. Fish and Wildlife Service, "Clinical Tests in Aquatic Toxicology: State of the Art"; Dr. Dean R. Branson, Dow Chemical Company, "Hazard Assessment of Chemicals in the Aquatic Environment"; Dr. Jerry F. Stara, Environmental Protection Agency, "Human Health Hazards Associated with Chemical Contamination of the Aquatic Environment"; and Dr. Kenneth J. Macek, E. G. & G., Bionomics, "Aquatic Toxicology: Fact or Fiction?". Approximately 900 persons attended the Symposium and participated in the panel discussion. The proceedings of the Symposium will be published in 1979 in an issue of Environmental Health Perspectives.

Professional Activities

Besides attending Executive Management courses, STEP seminars, courses at the Upward Mobility College, and other training and development courses, staff members presented the following papers, lectures, or seminars:

In February, Dr. Raymond E. Bahor, Executive Secretary, Toxicology Study Section, presented a talk on "The Grant Review Process and Preparation of an Application" to faculty and students at the University of Tennessee in Memphis.

On August 30, Ms. Carol A. Campbell, Executive Secretary, Social Sciences and Population Study Section, participated in a session for the Sociologists for Women in Society entitled, "Research Grants and Contracts: Funding Sources, Types of Funding and Writing Strategies." This session was held in conjunction with the annual meeting of the American Sociological Association

in Boston.

On January 3, Dr. D. S. Dhindsa, Executive Secretary, Reproductive Biology Study Section gave a seminar at the Postgraduate Institute of Medical Education and Research at Chandigarh, Punjab, India, and on January 5, gave a seminar on "In vitro Fertilization and Its Implications" at the Punjab Agricultural University, Ludhiana, Punjab, India. During the January 7-12 Seventh Congress of the International Primatological Society at Bangalore, India, Dr. Dhindsa participated in a symposium on "Nutrition and Nutritional Diseases" and presented a paper on "Effect of Breathing Carbon Monoxide (CO) on the Respiratory Characteristics of Blood of Cynomolgus Monkeys."

Dr. Michael F. Halasz, Executive Secretary, Communicative Sciences Study Section was an observer-participant at the Conference on Interrelations of the Communicative Senses, Asilomar, CA, September 29-October 2, and on October 18, he delivered an invited presentation on "Operant Conditioning Methods as Analytical Tools for Neurological Diagnosis" to the Department of Neurology, Mount Sinai Hospital, New York.

On February 28, Dr. Arthur S. Hoversland, Executive Secretary, Human Embryology and Development Study Section presented an invited paper, "Physiological and Endocrine Characteristics Which Make Sheep and Goats useful in Biomedical Research," at a symposium held at Salt Lake City, Utah, and sponsored by the American Association for Laboratory Animal Science.

Dr. Asher Hyatt, Assistant Chief, Biomedical Sciences Review Section gave a presentation on "The Search for Excellence -- the Peer Review System" during the October meeting of the American Chemical Society held in Fayetteville, AR. He also chaired a symposium on "PHS Goals and Missions in Medicinal Chemistry" at the September American Chemical Society meeting in Washington, D.C.

On October 3, Dr. Joseph A. Kaiser, Executive Secretary, Pharmacology Study Section presented a seminar at Vanderbilt University on "The NIH Grant Review Process: The Application Preparation, Peer Review, and Funding Process."

During the State University of New York Statewide Meeting on Research Involving Human Subjects, December 11-12, Dr. Miriam F. Kelty, Executive Secretary, Human Development Study Section presented the Federal view for the 2-day meeting of chairpersons of Institutional Review Boards from all campuses of SUNY, and during the Eastern Psychological Association/American Psychological Association meeting on April 20, she presented the workshop on Professional Issues, focusing on ethics of research and protection of human subjects, for state psychological associations, university administrators, and researchers.

At the Second International Congress on Patient Counselling and Education held in the Hague, The Netherlands, in May Dr. Kelty presented a lecture entitled "Ethical Issues and Guidelines: Health Care and Health Research." Delegates from 21 Nations attended this meeting which concentrated on psychosocial aspects of health and illness.

During the September American Psychological Association meeting held in New York, NY, Dr. Kelty delivered the Presidential Address on "Ethics of Research: Policy Paradigms and Paradoxes" to the Division of Population and Environmental Psychology. Dr. Kelty also participated in the panel on "Declining Fertility: Psychological Research Frontiers" and chaired the Executive Committee meetings and business meetings of psychologists in public service, the Division of Population and Environmental Psychology, and the Division of Health Psychology.

Dr. Betty June Myers, Executive Secretary, Tropical Medicine and Parasitology Study Section, was chairman of the Centennial Meeting and of the Special Paper Session at the meeting of the American Microscopical Society held in Richmond, VA, in December. In August, Dr. Myers was an invited speaker for a special symposium called "The Biology of the Trichurata" at the American Society of Parasitologists, Minneapolis, MN.

On February 9, Dr. Eileen C. Raizen, Executive Secretary, Microbial Chemistry Study Section, presented a seminar entitled "Grants Peer Review Process at NIH" at the Department of Biological Sciences, University of Denver, and the Denver Research Institute, Denver, CO.

In December, Dr. Thomas M. Tarpley, Executive Secretary, Oral Biology and Medicine Study Section, spoke on "Salivary Gland Swellings" to the residents and staff of the U.S. Naval Dental School in Bethesda, MD. From December 11-13, Dr. Tarpley gave a special course entitled "Salivary Gland Pathology of the Head and Neck" at the Armed Forces Institute of Pathology with the Department of Otolaryngic Pathology and the Department of Oral Pathology in Washington, D.C. Also during December, he presented a lecture on "Review of Grantsmanship and the Peer Review System" at the Medical College of Georgia, Augusta, GA.

In January, Dr. Tarpley gave a short course on "Non-Neoplastic Sialoadenopathies" at the National Naval Dental Center, Bethesda, MD, and from January 19-20, he gave a lecture and laboratory session (Oral Carcinoma - Odontogenic Lesions, and Salivary Gland Tumors) to sophomore medical students at the Uniformed Services Medical School in Bethesda, MD.

Dr. Tarpley was the guest speaker for the Scientific Program of the Charleston, South Carolina, Dental Society in February. On March 9, he gave a lecture on "Non-Neoplastic Sialoadenopathies" at the 26th Annual Course in Oral Pathology, Armed Forces Institute of Pathology, Washington, DC, and on March 12, presented a seminar on "Neoplastic and Non-Neoplastic Lesions of Salivary Glands" at the Medical University of South Carolina Dental School, Charleston, SC. Dr. Tarpley led a graduate seminar on "Salivary Glands Function and Dysfunction" on March 28 at the Georgetown University School of Dentistry Graduate Seminar held in Washington, D.C., and on March 30, delivered a presentation on the "Mechanisms of Peer Review" at the Navy Breakfast -- IADR Meeting in New Orleans, LA.

On May 17, Dr. Tarpley presented a lecture on "Extramural Trends and Peer Review at NIH" at the Harvard School of Dental Medicine, Boston, MA.

Dr. Ann Schluederberg, Executive Secretary, Epidemiology and Disease Control Study Section prepared a paper entitled "Host-dependent Modification of Rubella Virus Polypeptides," with Dr. H. Lalitha Kumari which the latter presented at the 79th Annual Meeting of the American Society for Microbiology held in Los Angeles, CA, on May 4-8.

The executive secretaries were the authors, co-authors, or editors of a number of publications that became available during the year under review:

Bradley, D. E., Raizen, E., Fives-Taylor, P., and Ou, J. (Eds): PILI International Conferences on Pili, Washington, D.C., 1978, 371 pp.

Brodie, A., and Brodie, H.: "Aromatase Inhibitors and their Use in Controlling Estrogen-dependent Processes." J. Steroid Biochem. IN PRESS

Brodie, A. M. H., Wu, J. T., Marsh, D. A., and Brodie, H. J.: "Antifertility Effects of an Aromatase Inhibitor, 1,4,6-androstatriene -3,17-dione." Endocrinology 104:118-121, 1979.

Dhindsa, D. S., and Hoversland, A. S.: "Respiratory Characteristics and 2, 3-diphosphoglycerate Concentration of Dog Blood during the Postnatal Period." Comparative Biochemistry and Physiology IN PRESS

Dhindsa, D.S., Hoversland, A. S., and Metcalfe, J.: "Resting Hemodynamics and Oxygen Transport in Unanesthetized Adult Cats." Respir. Physiol. IN PRESS

Dhindsa, D. S., Metcalfe, J., and Malinow, M. R.: "Effect of Breathing Carbon Monoxide (CO) on the Respiratory Characteristics of Blood of Cynomolgus Monkeys." Proceedings Seventh International Primate Society 37, 1979

Henkin, Robert I., Lippoldt, Roland E., Bilstad, James, Wolf, Robert O., Lum, Clark K. L., and Edelhoch, Harold: "Fractionation of Human Parotid Saliva Proteins." JBC 253:7556-7565, 1978

Hoversland, A. S.: "Characteristics which make Sheep and Goats Good Models for Biomedical Research -- Physiological and Endocrine." Symposium: The use of Sheep and Goats in Biomedical Research IN PRESS

Hoversland, A. S.: "Maternal Cardiovascular Adjustments during Pregnancy in the Goat." Proc. of VII Reunion of Asociacion Latinoamericana De Produccion Animal, Panama City, Panama IN PRESS

Hoversland, A. S., Dhindsa, D. S., Murphy, W. S., and Metcalfe, J.: "Respiratory Properties and 2, 3-diphosphoglycerate Concentrations in Blood of the Adult Opossum (Didelphis Virginiana)." Comp. Biochem. and Physiol. IN PRESS

Hoversland, A. S., Metcalfe, J., Dhindsa, D. S., Gabbe, S. G., and Porter, G. A.: "The Influence of Progestin Administration upon Hemodynamics in Castrate Male Pygmy Goats. Am.J. Vet. Res. 38: 559-563, 1979.

Jacobs, M. S., McFarland, W. L., and Morgane, P. J.: "The Anatomy of the Brain

of the Bottlenose Dolphin (Tursiops Truncatus). Rhinic Lobe (Rhinencephalon): the Archicortex." Brain Res.Bull. 4 (Suppl. 1): 1-108, 1979.

Kelty, M. F.: The Handbook of Futures Research, Fowles, J. (Ed.). Book Review in Science, Technology, and Human Values, Summer 1979.

Kelty, M. F.: "Health Technology Assessment and Impact." National Forum, 27-31, Fall 1978.

Kelty, M. F.: "The Protection of Subjects and Encouragement of Applied Research," in Preservation of Clients Rights. Hannah, J. T., Clark, H. B., and Christian, W. P. (Eds.). The Free Press/MacMillan Publishing Co. IN PRESS

Kelty, M. F.: "Part III: Welfare of the Research Subject," in Ethical Issues in Sex Therapy and Research, Volume II: Kolodny, R. C., Masters, W. H., Johnson, V. E., and Weems, S. M. (Eds.) Little/Brown Publishing Co. IN PRESS

Malinow, M. R., McLaughlin, P., Dhindsa, D. S., Metcalfe, J., Oschner III, A. J., Hill, J., and McNulty, W. P.: "The Effect of Carbon Monoxide on Diet Induced Atherosclerosis in Cynomolgus Monkeys (Macaca Fascicularis)." In Tobacco and Health, American Medical Association Education and Research Foundation 138, 1978.

Marafie, E., Nayak, R. K., and Alzaid, N.: "Breeding and Reproductive Physiology of the Desert Gerbil, Meriones Crasus." Laboratory Animal Science 28: 397-401, 1978.

McFarland, W. L., Jacobs, M.S., and Morgane, P. J.: "Blood Supply to the Brain of the Dolphin, Tursiops Truncatus, with Comparative Observations on Special Aspects of the Cerebrovascular Supply of other Vertebrates." Neurosci. and Biobehav. Rev. 3 (Suppl. 1): 1-93, 1979.

Myers, B. J.: "Anisakine Nematodes in Fresh Commercial Fish from Waters along Washington, Oregon, and California Coasts." Journal of Food Protection 42:380-384, May 1979.

Nyak, R. K.: "The Fine Structure of the Camel Corpus Luteum of Early Pregnancy and After Parturition." Ninth International Congress of Electron Microscopy, Tronto, Canada, Volume II: 558-559, 1978.

Nayak, R.K.: "Studies on the Ultrastructure of the Sow Oviduct Epithelium in Different Functional States." J. Univ. of Kuwait 5: 93-104, 1978.

Nayak, R. K. and Kassira, W. N.: "Correlated Scanning and Transmission Electron Microscopy of Camel Oviduct." J. Univ. of Kuwait 5: 105-113, 1978.

The Statistics and Analysis Branch (SAB) is involved in almost every facet of NIH's extramural activities. Through its IMPAC System (a central data system on extramural activities), the Branch performs services at virtually every stage of application processing, from initial receipt through the final award. SAB assists the Referral Branch by providing every 2 weeks a microfilm containing information on all applications, awards, and contracts recorded in the system, and the Scientific Review Branch by providing various documents, such as the resume of IRG Actions and the Application Summary Statement (Pink Sheet). SAB also assists the national advisory councils, as well as the awarding units, by providing such services and documents as the resume of Council Actions and the Notice of Award with accompanying Approval List.

While providing these services, the Branch is at the same time developing a data base on the extramural activities of the NIH. This data base is used to support all levels of NIH management and to provide a source from which NIH can meet its reporting obligations.

SAB also operates a sophisticated computer disk storage and retrieval system, CRISP. CRISP (Computer Retrieval of Information on Scientific Projects) maintains scientific information, under approximately 7,900 subject headings, on all PHS-supported research projects by fiscal year back to fiscal year 1971. CRISP generates the annually published 2-volume Research Awards Index that lists every research project supported by the Public Health Service. Volume I provides a fully cross-referenced subject index of currently supported research. Volume II lists (1) project identification data (which include project number, title, and name and address of principal investigator), (2) a separate contract section, and (3) a final section listing project investigators alphabetically, followed by their associated project numbers.

Through its two major information systems, IMPAC and CRISP, and other smaller systems, SAB provides information services on extramural programs to all levels of NIH management, other Government agencies, and the public at large.

1. Office of Systems Planning

The Office of Systems Planning continued its efforts to improve the IMPAC System and to expand services to its users. In addition to new systems and systems modifications described below within the various reports of the individual sections of the Branch, the Office expended major efforts on the following:

Systems specifications were developed and formalized to create an NIH registry of recombinant DNA investigations. The registry will provide administrative and scientific information on all NIH-supported recombinant DNA investigations that are subject to the NIH recombinant DNA guidelines. The registry will have the capability of describing the specific cloned gene or gene sequence, the derivation of the DNA, the organism involved, the host-vector system, and the physical and biological containments required. The system should be ready for

implementation early in fiscal year 1980.

·The previous DNA Tracking System was redesigned to reflect major changes in the recently issued NIH guidelines for research involving recombinant DNA molecules. Initial review groups are no longer required to assure that proposed applications comply with the NIH guidelines. On the other hand, modified footnoting of the IRG worksheets, pink sheets, resumes, and the Notice of Grant Award will be retained.

·The office spearheaded a major comprehensive study of the application review process within the DRG study sections. The report of the study team made significant recommendations for the acquisition and installation of word processing equipment and the establishment of a prototype service unit capable of handling the typing needs of approximately 20 study sections. The use of the new equipment, to be installed by the end of the fiscal year, plus the microfilming of office files, is intended to substantially reduce the heavy clerical workload and overtime now experienced by the DRG study sections.

·The implementation of the new Federal Procurement Data System in October necessitated a major modification in SAB's contract data collection and reporting requirements. The new system involved collection of additional contract information as well as the redefinition and recoding of some data already contained in the IMPAC system. The office also developed and implemented a system for the monthly transfer of research contract information to the Public Health Service which it, in turn, provides to the DHEW for the Federal Procurement Data System.

·The NIH Grants Management/ICMS Worksheet, Form 705, has been redesigned for the computer preparation and will be utilized as an integral part of the grant award process as soon as printed copies of the form become available. The form, with data printed from IMPAC, will be sent to the BID grants management officers for use in the preparation of Award Notices. The computer printed form will negate the manual completion of many items by the grants management officers and specialists and will replace the Notice of I/D Action Form.

·Table 4 of the IMPAC Central Table System, which contains the titles of the NIH Initial Review Groups, was expanded to include the 5-digit identification number of the Committee Management Information System (CMIS). Inclusion of the CMIS number in the table provides a means for directly linking IMPAC records to records within the Committee Management System. In addition, title editing where necessary was introduced to enhance the presentation and reporting of IRG information.

2. Data Processing Section

Pre-Award Contract Information. A computer file has been established within the IMPAC System to store pre-award information relative to proposed new negotiated research contracts and "renewal" of existing contracts for which a Request for Contract (RFC) has been approved.

Sub-project System. The first phase of the sub-project system became operational this year. The initial file contains a computer record for each IRG

approved research grant application which involves sub-projects.

New IMPAC Items. The following items were added to the IMPAC System data base during the past year:

·Estimated number of Predoctoral Trainees for Future Years

·Estimated number of Postdoctoral Trainees for Future Years

·Agency Code (NIH,ADAMHA, etc.)

·Date Application was Inactivated or Withdrawn

Random Access for Institutes and Divisions (RAID) Routine. The RAID routine, which allows direct access to individual records in the IMPAC System, was expanded to allow the BIDs to randomly access dual assignment records in which they are the secondary BID and records transferred from their BID to another BID.

DFM/DRG Computer Link. Because of a change in the individual fellowship payment mechanism, fellowship records in the IMPAC System are now being updated directly from the DFM/DRG link tapes. Under the new method of payment, awards are made to the grantee institution which in turn, pays the fellow.

Trainee Appointment File. The Trainee Appointment File was redesigned this year. The new file is stored on-line and contains trainee appointment records for several years. As a result, more information is now available on indirect trainees supported under NIH, ADAMHA, and other PHS training grants.

Verification List of Trainees. A computerized list of trainees for whom PHS has received a Statement of Appointment of Trainee Form (PHS 2271) is now being produced by the Section. This listing is forwarded to the training grant program directors for verification. The primary purpose of this process is to ensure that the records at PHS are complete and accurate. This is particularly important since the Statement of Appointment Forms serve as the base document for calculating an individual's payback obligation for trainees supported under a National Research Service Award.

3. Research Documentation Section (RDS). The Section maintains a computerized disk storage and retrieval system, CRISP (Computerized Retrieval of Information on Scientific Projects), containing scientific data on research grants and contracts supported by the Public Health Service and NIH and NIMH intramural research. Through this medium, RDS responds to ad hoc and recurring requests for scientific information from Government administrators, scientists, and information personnel for purposes such as analysis and evaluation of research programs, specific scientific areas, and preparation of reports. Similarly, the Section responds to inquiries from grantee and nongrantee institutions and scientists, the news media, and other non-Government sources engaged in, concerned with, or reporting on medical research.

RDS publishes annually as a "spin off" of the CRISP file:

1) The Research Awards Index prepared in two volumes. Volume I is a scientific subject index with associated project numbers and titles. Volume II contains three sections: (a) project identification data, (b) research contract identification data, and (c) project investigator information.

2) The Medical and Health Related Sciences Thesaurus, the vocabulary authority list of subject headings used by the RDS indexing staff in indexing research projects.

CRISP has the query capability of (a) providing, in several optional formats, information ranging from a straightforward listing of research pertaining to a single scientific subject term to a compendium of projects relating to any number of terms, using a combination of Boolean search logic: (b) furnishing individual institutes with tapes or hard copy of their projects by subject, project (subproject), title or name of investigator, and (c) generating individual institution/institute listings of projects with indexing terms (Scientific Profiles). CRISP also has the query capability to limit subject searches or Scientific Profiles to certain program (R, M, N, P, S, Z) or IPF codes.

A specially designed CRISP subroutine can supply grantee institutions or NIH institutes possessing appropriate computer capabilities with specially formatted tapes which they can use to search the scientific subject content of their own research grant and contract records. This subroutine called CESI (CRISP Extract System for Institutions/Institutes) is updated monthly and can furnish select tapes on an ad hoc or recurring basis.

Subproject Information. A significant feature of the CRISP system is its capability of subdividing program projects, center, and other large projects into their individual research components thereby providing more detailed and accurate information of the research objectives of these large grants, in addition to the names of principal investigators conducting the research.

CRISP Services. During fiscal year 1979, the Section responded directly to nearly 1200 requests on a wide range of subjects; prepared linotron tapes used in the creation of extract Indexes and related material for nine institutes; provided Scientific Profile data reports and/or CESI tapes for grantee institutions; furnished NIH-wide scientific area data for appropriate institutes; and performed professional editing operations involving thousands of approved research grant and contract applications. In addition, the Section played a significant role in providing material on various trans-NIH issues such as diabetes, arthritis, genetics, nutrition, hematology, gastrointestinal diseases, cystic fibrosis, pregnancy, behavioral sciences, health care, and rehabilitation.

Intramural Research Projects. Professional indexing and entry into CRISP of scientific keyword, title and principal investigator data from fiscal year 1978 intramural research projects was completed in March. This information was subsequently published in the annual NIH-NIMH Intramural Research Index.

Research Awards Index (DHEW Publication No. (NIH) 79-200). New programs developed within the Statistics and Analysis Branch greatly facilitated the

creation of Linotron tapes for production of this and related publications.

On-line access. A number of NIH institutes are directly accessing CRISP file 5 which contains project narratives for PHS grants and NIH contracts, as well as intramural research conducted by NIH and NIMH. Information from this component of CRISP, which is limited to DHEW use only, is also furnished in hard copy format to several other institutes. Currently, some institutes are also accessing CRISP subject files on-line. It is requested that RDS be contacted each time before running subject searches to assure that optimal results are achieved.

4. Reports, Analysis, and Presentations Section. The primary function of the Section is to satisfy the information requirements of NIH and PHS centralized extramural activities. In fulfilling this function, the Section utilizes the IMPAC system, as well as other data sources. Its responsibilities include: design, maintenance, and operation of computer reporting systems; training and technical assistance in data retrieval; planning and coordination of NIH responses to annual surveys covering Federal obligations for R and D; preparation of formal publications such as listings of NIH grants and awards and the NIH Basic Data Booklet; statistical analysis to compile and present visual materials dealing with extramural trends or other topics; and the development and implementation of special evaluation projects. This Section also works closely with the Data Processing Section in maintaining and extending the IMPAC system, and has direct responsibility for establishing institution classifications and related computer files, as well as ensuring the accuracy of selected key data items for publication or reports.

Publications. The following volumes of listings of NIH extramural awards were issued:

(1) National Institutes of Health Research Grants, FY 1978 (DHEW Publication No. (NIH) 79-1042)

(2) National Institutes of Health Grants for Training, Construction, Cancer Control, Medical Libraries, FY 1978 (DHEW Publication No. (NIH) 79-1043)

(3) National Institutes of Health Research and Development Contracts, FY 1978 (DHEW Publication No. (NIH) 79-1044)

The following volumes of the annual multi-volume series on PHS Grants and Awards were issued:

(1) Public Health Service Grants and Awards, Part I, FY 1977 Research Grants (DHEW Publication No. (NIH) 78-1133)

(2) Public Health Service Grants and Awards, Part II, FY 1977 Training, Health Manpower Education, Construction, Medical Libraries (DHEW Publication No. (NIH) 78-1134)

(3) Public Health Service Grants and Awards, Part III, FY 1977

Health Planning and Health Services Grants (DHEW Publication No. (NIH 78-1135)

Data for the pocket reference book, Basic Data Relating to the NIH-1979 (NIH Publication No. 79-1261) were compiled in cooperation with the NIH Office of Program Planning and Evaluation. This publication presents information on the programs and resources of the NIH.

Special Statistical Presentations. The Section compiled and analyzed extramural program statistics for fiscal years 1968-1978, and participated with the Chief, Statistics and Analysis Branch, in developing a set of 35mm slides illustrating key extramural trends. These slides were presented formally to the Director, NIH, and other officials, and subsequently to various additional audiences. The data were also issued, with an accompanying analysis, in a chart-book entitled NIH Extramural Trends, Fiscal Years 1968-1978 .

Research and Development Activities. The annual survey conducted by the National Science Foundation, entitled Federal Funds for Research, Development, and Other Scientific Activities, is coordinated and prepared by this Section for the entire NIH. In general, the survey covers all the NIH intramural and extramural research activities for the past fiscal year along with the estimated obligations for the next 2 fiscal years, by performer, field of science, geographic area, basic and applied research and development, and combinations of the above. The Section is responsible for obtaining and maintaining data from the BIDs which indicate the amount of basic and applied research and development for each research grant and R & D contract. At the request of OD, breakouts of Clinical Trials and Transfer Activities (required by NIH for SATT reporting) are also maintained in this special system.

Special Staff Support to Outside Offices. The Section prepared and interpreted data to assist the "NIH Task Group on Award Rates." This work led to the implementation of a standard procedure for computing award rates in response to mandates from the House Appropriations Committee.

Several simulation models were designed to show when and how NIH could stabilize the number of competing versus noncompeting research projects in connection with implementing the 5-year research plan for NIH.

Budget Hearings. A large variety of reports were prepared at the request of DFM covering estimated amounts needed to fund research project applications with priority scores of 250 or better; volume of research project applications reviewed, eligible for award, awarded, and award rates; distributions of awards by type of institution; average awards per principal investigator, and so on. These data were used to determine the adequacy of the NIH budget.

The CASE Report. The survey of DHEW obligations to institutions of higher education and other nonprofit organizations summarizes support to individual institutions. The NIH response to this survey is coordinated and prepared by this Section. It requires an institution-by-institution report of all NIH extramural support, by activity, for most nonprofit organizations, with an individual report for each health professional school. In addition,

data by field of science grouping and activity are also requested for institutions of higher education.

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

DIVISION OF RESEARCH RESOURCES

Fiscal Year 1979

ANNUAL REPORT

FISCAL YEAR 1979

(October 1, 1978 - September 30, 1979)

DIVISION OF RESEARCH RESOURCES

National Institutes of Health
Bethesda, Maryland 20205

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REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

Report of the Division Director

Early in fiscal year (FY) 1979, we embarked on a major effort to develop a Divisional Five-Year Program and Financial Plan, FY 1982-86. As FY 1979 draws to a close, the final results of the process thus set in motion are yet to be determined.

The Division's five Program Directors, their staff, and each of the advisory Initial Review Groups have been responding to a program planning concern set forth in the following charge:

Assumption

The DRR budget for the fiscal years 1980-86 will be constrained by a general "no growth policy" enunciated by the Administration and reinforced by the mood of the national electorate calling for reduced Federal spending. The Division's budget will suffer continued erosion due to inflationary pressures. In seeking an optimum balance between program stability and program initiatives among the five highly differentiated programs of the Division, budgetary trade-offs probably will be the basic budgetary processes used to seek such a balance.

Thesis

There are few if any precise objective measures to determine differences in the impact on the Nation's biomedical research effort between such disparate DRR Programs as--

- General Clinical Research Centers
- Biotechnology Resources
- Primate Research Centers
- Biomedical Research Support
  (formerly known as General Research Support)
- Minority Biomedical Support
- Laboratory Animal Sciences

Therefore, even in an era of fiscal constraints subjective measures continue to be important when dealing with the Division's program direction, budget formulation and execution. An increasingly important measure, however, is the skill that the Program and its advisors demonstrate in long range planning. Thus, Divisional funds will be allocated to those Programs that can best state their needs and opportunities in written plans indicating what scientific areas and priorities have been proposed to best use the scarce dollars.

Facts

The cost pressures within the General Clinical Research Centers Program has led to a phaseout of some five Centers over the past several years and other approved Centers may have to be phased out in the early 1980s.

The Biotechnology Resources Program has an approved unfunded backlog of approximately $2.5 million of high priority (135-212) national shared instrumentation resource applications in its portfolio and is in the process of phasing out several competing continuation resources with priority scores better than 200.

The Primate Research Centers have a decaying physical plant, one that was originally constructed through special Federal legislation (subsequently withdrawn) in the early 1960s. Thus, choices between program quality and required physical plant maintenance and replacement are becoming more critical each year.

The Minority Biomedical Support Program, the cornerstone in corporate NIH's extramural affirmative action program, is sustaining its momentum above its base appropriation only through a series of annually negotiated intra-agency transfer of funds from nine other Institutes of NIH. These of course are subject to downward negotiation based on the priorities of the other Institutes.

The Biomedical Research Support Program appropriation is currently running at a level some 12 to 13 percent below its legally authorized level of funding.

The Laboratory Animal Sciences (LAS) Program continues to have demand pressures on it by evolving regulations and public pressure regarding the care and use of animals used in research.

Modus operandi

A set of general questions as well as those that are program specific of a long range planning nature were developed. Such questions and their answers stimulated discussion and response and required elucidation from the DRR Program Directors of their thinking and that of the Division's advisory apparatus. This has lead to the identification in writing the key scientific and administrative needs, opportunities and issues facing each Program in the mid-1980s. The Program Directors are expected to develop from this written plan, addressing the prioritization of these issues, the proposed allocation of limited resources. Thus, how seriously and how well each Program articulates its program direction, goals, priorities, trade-offs, and resource allocations will critically affect Divisional budgetary recommendation to the Director, NIH.

The material received from the five highly differentiated Programs of the Division will undergo analysis and synthesis into a more integrated Divisional Five-Year Plan during the final months of FY 1979. This will be

subject to final review by the National Advisory Research Resources Council in late October 1979 and an operational review by the Director, NIH, early in FY 1980.

It is our current intention to make the Plan available to the extramural community we serve with an invitation for comments.

This final element of the Division's planning process will set the stage for future refinement of the DRR Five-Year Plan.

REPORT OF THE DEPUTY DIRECTOR

Dr. James F. O'Donnell

Report of the Deputy Director

During Fiscal Year 1979 all vacancies on the National Advisory Research Resources Council were filled in a timely manner and all of the Council Program Work Groups became functional at the May meeting. We had made advanced plans to hold the May meeting in Atlanta where the Council would have the opportunity to visit a large MBS Grantee Institution, a Primate Center, a General Clinical Research Center, and several Biomedical Research Support Grant Institutions. This would have afforded both Council and staff members with an opportunity to become acquainted with resources funded by the Division with which they had minimal on-site familiarization. Due to restrictions on staff travel, however, it was not possible to carry out these plans. We hope to reschedule this activity during the coming Fiscal Year.

The merger proposed two years ago of the Animal Resources Advisory Committee with the Primate Research Center Advisory Committee into a single Committee, the Animal Resources Review Committee, was approved by the Department in May of this year. We were instructed, however, to reduce the full Committee membership from 23 to 20 by June 30, 1980. We are confident a membership of 20 will provide the Committee with sufficient expertise for adequate review of all assigned applications. The first meeting of the merged Committee was held on May 30, 1979, at which orientation for the full range of the Animal Resources Program activities was provided.

The first joint meeting of the two subcommittees making up the General Research Support Review Committee, the Minority Biomedical Support Subcommittee and the Biomedical Research Support Subcommittee, was held on June 28, 1979. This provided an opportunity for Program staff to explain the Minority Biomedical Support, Biomedical Research Support Grant and Biomedical Research Development Grant Program objectives and application review criteria to members who had previously participated in only one of the Program activities.

From discussions generated among members of the Division's Review System Group a policy statement was developed concerning the acceptance of food and refreshments by staff and consultants during staff or site visits. The policy, which was accepted and promulgated by the Director, DRR, states that:

> "In interpreting the HEW Standards of Conduct, /Subpart C, 'Gifts, Entertainment and Favors,' No. 73.735-301 and No. 73.735-305/, no DRR employee may accept food, entertainment or other gratuities from members of the public with whom the DRR employee has an official relationship, e.g., a grantee, an applicant or a potential applicant. Acceptance of light refreshments (e.g., coffee, soft drinks, donuts, etc.) is excluded from this definition.

"If required for the efficient conduct of a project site visit or staff visit, arrangements may be made for the institution to provide lunch (or other meal) for which the host will be reimbursed by prorating the cost among DRR staff and consultants. The responsible DRR employee should inform the institution of this policy at the time the visit is arranged.

"Offers by the applicant, grantee, or potential applicant to provide entertainment, sight-seeing tours, etc., prior to or subsequent to the official visit must be politely refused by the staff and consultants."

Adherence to this policy, we believe, removes staff and consultants from the possibility of any charges of conflict of interest in the discharge of their duties and does not place a grantee or applicant in the position of feeling he must "entertain" a review team. The Director, DRR, has sent this policy to the Associate Director for Extramural Programs to consider for adopting as NIH-wide policy.

Increasing numbers of requests from applicants, under the provisions of the Privacy Act, for summary statements prior to Council action are being received. Very few rebuttal letters or requests for reconsideration by the initial review group, however, have resulted subsequent to release of these summary statements. It would appear that the chief purposes for the requests are for early planning by the applicant--building up or phasing down a research effort or the preparation of a revised application. DRR policy with respect to rebuttal letters based on issues related to the initial scientific, technical merit review, is that such letters will not be brought before the National Advisory Research Resources Council. If the applicant wishes, the proposal will be returned to the initial review group for re-review.

As part of the reorganization of the former DRR Office of Program Analysis, two program analysts were assigned to the Deputy Director as a Special Projects staff. In addition to preparing responses to continuing requests from Trans-NIH Committees for analyses of scientific projects supported by DRR Programs, completely revised annual progress report forms for each of the five DRR Programs were drafted this year. Following approval by the Department and the Office of Management and Budget, the new forms will be used by DRR grantees for reporting yearly scientific progress. The revised forms hopefully will permit us to obtain, process, and analyze program data more quickly and accurately.

In Fiscal Year 1980 the Deputy Director's emphasis will be to maintain and improve the quality of program management, program analysis and initial scientific review.

DRR PROGRAM/OFFICE REPORTS

Fiscal Year 1979 has marked significant expansion of the concept of the Research Resources Information Center. The Office established the Center in 1976 and has offered project and technical guidance since that time. The objective of the RRIC is to promote the awareness of, the value of, the utilization of, and the access to DRR-supported research resources.

The further development of the Research Resources Reporter, the Center's regular print contact with scientists throughout the United States, was evinced this year by a substantial increase in circulation (mail and newsstands); by requests for reprints from such organizations as the National Society for Autistic Children, Yale University, Johns Hopkins University, the University of Virginia, the National Institute of Arthritis, Metabolism, and Digestive Diseases, and the Albany Medical Center; by a publication award from the National Association of Government Communicators; by reference to the Reporter in the Washington Post and other publications; by acceptance of the RRIC staff-written articles in professional trade publications; and by hundreds of favorable comments from scientists and administrators throughout the country--and NIH personnel at all levels.

Early in the year, a readership response form indicated conclusively that the Reporter is fulfilling its mission. A total of 1,285 readers responded to an address information form in the January issue. Approximately 99 percent of the respondents indicated they wished to continue receiving the monthly newsletter; 88 percent said they read at least 50 percent of each issue; and 98.3 percent agreed that the Reporter serves a useful line of communication among researchers.

A sampling of hundreds of favorable comments attested to the reaction of the reading audience:

University of Kansas - "I appreciate the coverage of research projects."

University of Pennsylvania - "This is an excellent publication. Keep up the good work."

Boston Biomedical Research Institute - "Mix is well chosen."

Bowman-Gray School of Medicine - "It is very good as it is."

University of South Carolina - "Give us more of the same."

Rider College - "It's almost perfect."

G. C. Searle & Company - "Great! Keep it up."

V. A. Hospital, California - "Extremely valuable."

University of Notre Dame - "I believe that the Reporter serves a useful role as a translator from a specialized researcher to an intelligent decision maker."

University of Texas - "I believe that you are doing an excellent piece of work."

NIH, Bethesda - "I enjoy and profit from present format."

NIH, Bethesda - "I like the present format, especially the research news."

The article, "Research Into Autism Yields New Insights," which appeared in the November 1978 Reporter, prompted the National Society for Autistic Children to request a large number of reprints for distribution "to parents and professionals at our regional and annual NSAC meetings." The Society also indicated they will be sending the reprint to individuals and institutions who purchase books from their bookstores.

The Reporter was also cited by the Washington Post (May 14, 1979) as an authoritative source by author James T. Yenckel. In his article on autism, Mr. Yenckel used quotations from the Reporter, giving full credit to the source.

Yale University, Johns Hopkins University, and the University of Virginia requested large numbers of reprints of the article, "Psychosocial Dwarfism and Child Abuse" from the July 1978 Reporter.

The Albany Medical College of Union University also requested reprints from the February 1978 Reporter concerning the new shock trauma techniques developed by their unit.

The National Institute of Arthritis, Metabolism, and Digestive Diseases requested reprints from the Reporter January 1979 story, "Physicians Search For Cause of Lyme Arthritis," and also from the February 1979 story, "New Test For Connective Tissue Diseases."

The monthly distribution of the Reporter continued to rise. It has gone from an initial 3,875 (January 1977) to 14,000 as of August 1979. This figure includes distribution in the U.S. and to 118 recipients in 41 foreign countries and in Puerto Rico.

The newsletter's visibility and circulation were considerably increased by additional newsstand distribution in Bethesda, and just recently at several grantee facilities. The idea for the newsstands was developed by OSHR. At present, there are nine Reporter newsstands on the NIH campus, in the Federal Building, the Landow Building, and at the Westwood Building.

The first out-of-town newsstand distribution was made during the past year. There is now a Reporter newsstand at the Schools of Medicine, University of California, San Diego, and at the University of California, San Francisco. The San Diego campus has requested another newsstand for their library entrance.

The total monthly distribution through 13 newsstands is now over 5,000.

In May, the National Association of Government Communicators gave the 1979 Second Place Blue Pencil Award to Jim Augustine, DRR Information Officer, citing the Reporter as an Outstanding Government Publication in the Newsletter Category. There were over 500 entrees submitted (in all categories) for the coveted Blue Pencil awards.

In addition to activities associated with Reporter publication, a total of 6,980 inquiries were received by the RRIC during the year. These included requests for directories, requests to be put on the Reporter mailing list, and a wide variety of mail and telephone inquiries on the subject of research resources.

The 1979 revisions of the Biotechnology Resources Directory, the Animal Resources Directory, and the Minority Biomedical Support Directory were produced and distributed during the fiscal year. The revised General Clinical Research Centers Directory is scheduled for distribution in the fall. The design and format of the 1979 directories has been changed to make for a more attractive and useful reference book. The distribution of the directories varies from 6,000 to 8,000 each.

To further promote the visibility and distribution of the RRIC products, OSHR designed and produced a special Research Resources Information Center table top exhibit. This attractive exhibit is designed to display the latest issues of the Reporter and all of the DRR Directories, in addition to the DRR program brochure.

During the latter part of the fiscal year, the RRIC has been working on the first of a series of special scientific publications based upon the research activities of DRR grantees. The publication will be entitled, Artificial Intelligence in Medicine, and will include input from the directors and principal investigators involved in DRR's Stanford University Medical Experimental Computer-Artificial Intelligence in Medicine (SUMEX-AIM) program. Printing is expected in the fall.

The OSHR office has been successful in making additional placements of outstanding articles appearing in the Reporter. Negotiations with the editors of Medical Tribune (155,000 circulation weekly) resulted in an agreement to publish medical articles from time to time in their entirety with full credit to DRR and the RRIC staff. Thus far, articles have appeared in the Medical Tribune on liver transplantation and on emotional dwarfism.

Lab Animal (over 14,000 bimonthly circulation) has run two RRIC-originated stories on the Giant Axon Squid, and on the Sloan-Kettering mice communication chemistry study.

An arrangement has been made with Newspaper Enterprise Association, national syndicate serving 750 newspapers throughout the country, to issue slightly condensed versions (800 words) of RRIC-originated stories. The first NEA syndicated wire story, sent out in July 1979, was on the bee venom studies at Johns Hopkins and the Mayo Clinic.

Public Health Reports (14,000 monthly circulation) has indicated their intention of publishing the RRIC story on lyme arthritis.

In other varied program promotional and informational activities, the OSHR has concentrated on expanding DRR program coverage by planning and participating in media briefings and special media events at DRR-funded resources. In addition, Office staffers have established a successful pattern of combining DRR regional and national program director meetings, administrative coordinator meetings, and nurses and dietitian meetings with radio, TV, and newspaper placements.

The Office made special efforts during the past year to encourage grantee institution information officers and program directors to report good science at their facility.

The effectiveness of these endeavors was evinced by a substantial number of locally-produced feature stories in various house organs throughout the country, by increased numbers of locally-produced releases, with full DRR credits, and by increased interest from DRR grantees in voluntarily calling or writing the Office to suggest potential media briefings in their city.

In the special event and press briefing activity area, the Office assisted Dr. John Markley, program director of the Purdue University nuclear magnetic spectrometry laboratory, in planning their formal dedication in West Lafayette, Indiana in November. The Office staffer also met with the Purdue University information officer to discuss promotional activities for the affair. The dedication, which featured Dr. James O'Donnell, DRR Deputy Director as the keynote speaker, was further publicized by a Purdue release, placements in the Indianapolis Star, the Purdue Exponent, the Lafayette Courier, and transmission of a 3-minute videotape from six television stations in the Indianapolis area.

In February, the Office held a media briefing at Albuquerque in cooperation with the University of New Mexico to describe new developments on a tiny insulin pump being tested at the clinical research center. The University had called OSHR and requested help in organizing a briefing for the New Mexico media. OSHR assisted with the preparation of press kit material and media contact work in the Albuquerque area. The media briefing was attended by eight Albuquerque media outlets, and the resulting coverage went well beyond the borders of New Mexico. Attending the media briefing were three TV camera crews, two radio station representatives, and three reporters from local newspapers.

In addition, the OSHR staffers personally visited the Albuquerque bureaus of the Associated Press and United Press International. The story and photos were sent across the country on both wire services. All area TV stations were supplied with a videotape of the briefing, and a wrap-up release was mailed to all newspapers and most of the radio stations in New Mexico.

In March, OSHR held a media briefing at the New Orleans Chamber of Commerce concerning a hypertension treatment compliance project being carried out through the MBS at Xavier University. In addition to the media briefing, the principal researchers were interviewed on several New Orleans area TV stations and radio shows. The story was also carried on the AP and UPI wire services. OSHR staff prepared press kits and made contacts with the local press and broadcast media.

Drs. Sidney McNairy (DRR program staff), Marcellus Grace, and Michael Thompson were the principals at the press briefing which was attended by TV, press, and radio representatives. The OSHR arranged for the taping of a 15-minute segment for "Perspective in Black" on WWL-TV with Drs. Grace and Thompson; a 10-minute live appearance of the two researchers on "Journal," Station WYES-TV; and appearances on "To Your Good Health" on WWL-TV, "Spectrum 50" at WDSU-TV, and "Good Morning New Orleans," among other TV and radio appearances. An interview with Dr. Grace and an Xavier student was taped and carried by the Mutual Black Network over 80 stations.

A GCRC progress report spotted by OSHR triggered a press briefing at the University of Rochester in May. A specially designed air-tight chamber at Strong Memorial Hospital is being used to test how airborn pollutants affect human bodies. The Rochester briefing was organized and executed by OSHR with the assistance of the University of Rochester public relations office. OSHR-prepared press kits were hand delivered to all Rochester media as well as certain key Washington-area media. The briefing was attended by local TV and newspaper representatives. Arrangements were made for Dr. Laurence Jacobs, GCRC director, to appear on WHEC-TV's "Noon at Ten" to discuss the pollutant chamber.

The Associated Press and United Press International wires carried the story. Lou Adler's "Report on Medicine" on CBS Radio, heard in the Washington area on Station WTOP, featured Dr. Jacobs discussing the chamber.

A 90-second videotape showing the pollution chamber, produced by OSHR, was mailed with a script to all commercial TV stations in New York State. A spot check indicated that more than half of these stations used the videotape.

The media activities for the Seventh Annual Minority Biomedical Support Symposium in Atlanta during April were highlighted by a continuous stream of radio and TV interviews set up by the Office staffers from the Press Room at the Atlanta Marriott Downtown Hotel. Individual telephone interviews for the Mutual Black Network from the MBS Symposium Press Room included Dr. Sidney McNairy, DRR; Dr. George Hillyer, University of Puerto Rico; Dr. Ciriaco Gonzales, DRR; Dr. Michael Thompson, Xavier University; Dr. Rosalind Cropper, graduate of Southern University; and Dr. Cyril Moore of Morehouse College.

Dr. Gonzales, Dr. James Henderson, Tuskegee University MBS program director, and Xavier student Larry Lowe participated in a 30-minute MBS discussion on "A Second Look," a regional Educational Network program seen on eight educational TV stations in Georgia, Florida, Alabama, and South Carolina.

Dr. Clarence Clark of Morehouse College taped a 30-minute program on Radio Station WIGO and also made a 2-minute live appearance on "Noon News," on WSB-TV; Dr. Charles Huggins, Nobel Laureate from the University of Chicago, and Dr. Frank Hamilton of Atlanta University appeared on a call-in program on Radio Station WBS; Dr. Gonzales did a 3-minute live interview on Station WXIA-TV; Dr. Clarence Clark and one of his MBS students taped a 30-minute discussion on MBS for "Ebony Journal," Station WXIA-TV; Dr. Clark and a MBS student took part in a 30-minute show on Station WAGA-TV; and Dr. Michael Thompson and MBS student Pamela Freeman of Xavier did a 20-minute show on Radio Station WQXI.

The Associated Press interviewed Dr. Marcellus Grace for a story sent over the AP wire from Atlanta.

In addition to arranging the interviews, press materials on the MBS Symposium were hand delivered to the Atlanta media by the Office staff. During the Symposium, OSHR staffed the Press Room and gave assistance to press representatives covering the meeting, including the Atlanta Constitution, the Atlanta Journal, the Atlanta Daily World, the Atlanta Inquirer, the Atlanta Voice, Jet Magazine, and representatives from the broadcast media mentioned above.

The Office embarked upon a heavy speaker presentation series during the year commencing with a 3-man presentation to the National Advisory Research Resources Council on OSHR operations.

The next presentation was made by Jim Augustine and Bill Glitz at the Second National Conference of Administrative Coordinators in San Antonio, Texas (Sept. 19-23). Their topic was "Visibility--To Be Seen Is To Be Understood." A spin-off of the OSHR talk was the formation of the GCRC Administrative Coordinators Communication Subcommittee to encourage a steady flow of communication about GCRC research activities from GCRCs to OSHR.

In November, an OSHR staffer appeared at the Administrative Coordinators regional meeting in Oklahoma City. The RRIC Table Top Exhibit was on display at the meeting. Follow-up letters were sent out to ACs and also nurses and dietitians.

In December, Jim Augustine and Bill Glitz made a presentation before the Minority Biomedical Support Program Directors Meeting in Houston, Texas. The theme of the talk was on communication to the scientific community and the general public. The OSHR team also arranged individual media interviews for Drs. Ciriaco Gonzales and Sidney McNairy on Stations KPRC-TV, KTRK-TV, KHOU-TV, and Radio Station KPRC. The Houston Post interviewed Drs. Gonzales and McNairy and wrote a feature article on the MBS Program. In addition, the Informer and Texas Freeman and the Houston Chronicle did feature stories with a local angle.

In February, the OSHR presenters conducted a 12-person workshop sponsored by the Communications Subcommittee of the GCRC Administrative Coordinators in San Francisco. The presentation included a videotape talk by Dr. Bowery, and was geared to familiarize the ACs with the DRR information operation and to aid in the communication of information from the GCRCs to OSHR.

In February, Jim Augustine and Bill Glitz appeared before the Eta Sigma Gamma, a health educator honorary society at the University of New Mexico in Albuquerque, to deliver their presentation, "You Need To Communicate If You're Going to Educate."

Jim Augustine, DRR Information Officer, conducted a Freedom of Information Grants Training Workshop in November. A commendation for the presentation was made by the NIH Associate Director for Communications.

In addition to the creation of the RRIC Table Top Exhibit during the year, the OSHR office designed and produced a full-scale exhibit for the Biotechnology Resources Program. Called "Biotechnology Resources, New Technologies and Procedures for Biomedical Research," the full-size exhibit is arranged to attractively display the Biotechnology Resources directory, PROPHET literature, DRR literature, or any associated Biotechnology Resource material to be produced and distributed in the future. The exhibit made its debut at the Federation of American Societies for Experimental Biology Convention in April at Dallas, Texas. Its second showing took place at the Annual Meeting of the Electron Microscopy Society of America in San Antonio, Texas on August 13-16, 1979.

Special exclusive articles were written and placed by OSHR during the year for such publications as Black Careers, Jet, Urban Health, Nuestro, Essence, the Mayo Alumnus, and Computers and Medicine.

During the year, the Office placed an article on CLINFO and a piece about Cincinnati's General Clinical Research Center studies on artificial fat in the Journal of the American Medical Association.

Further OSHR placements on DRR program activities included a cover photo for ILAR News of a Yerkes gorilla; a syndicated photo story sent over the wire by Newspaper Enterprises Association on the University of Texas Biomedical Institute's work on squid capture; HEW's NOW did a piece on GCRC centers; U.S. Medicine wrote stories on kepone detoxification at the Medical College of Virginia and on baking soda dosage treatment for short stature connected with a kidney disorder at the University of California Pediatric Clinical Center, San Francisco; MD Magazine told the story of amyloid studies on Celebes apes at the Oregon Regional Primate Research Center; a cover photo appeared in Lab Animal of another Yerkes gorilla; Children Today featured a full-page photo story on the NIH Primate Research Centers; and Vogue ran a consumer-slanted feature on the Cincinnati GCRC study on artificial fat.

During the year, the Office received and responded to over 30 individual mail requests for photos for use in publications throughout the country. To name a few, requests came from John Wiley & Sons, publishers of the book, Biology; the Journal, a newsletter of the Institute of Socioeconomic Studies; United Press International Science Services; Encyclopedia Britannica; Visual Education Consultants, Inc.; the Bulletin, Loyola Marymount University; the U.S. Information Agency; Omni Magazine; Forum on Medicine; Intercom, Duke University; Current Health Magazine; Medical Tribune; Life & Health; the publishers of the book Apes in Fact and Fiction; Medical Group News; Newsweek Books; and University News Service, University of Minnesota.

As the year drew to a close, a 2-minute videotape segment showing muscular dystrophy research at the University of Rochester General Clinical Research Center was being readied by OSHR for the nationally televised Jerry Lewis-Muscular Dystrophy Association Labor Day Telethon, telecast over approximately 215 stations throughout the country.

According to A.C. Nielsen Company, the Telethon, in 1978, was viewed by a national audience estimated at 88 million. It was rated the second most watched TV program in the U.S. last year.

OSHR originated the idea for the segment by contacting the Muscular Dystrophy Association, followed through by securing the cooperation of the GCRC personnel and investigators in Rochester, supervised the shooting of more than two hours of videotape by AV staff at the University of Rochester, and devoted several days to editing at the NIH TV studios.

The Muscular Dystrophy Association has also asked permission to use the videotape material for additional purposes following this year's telethon. OSHR has also arranged for the University of Rochester GCRC investigators to appear live on local breaks at the Rochester, New York TV Station, WHEC-TV.

In DRR publication-producing activities, the Office completely revised the popular foldout, Do We Care About Research Animals?, detailing the need and contributions of laboratory animals to biomedical research. A mailing and release was made to all laboratory animal grantees and to the veterinary interest press. The revised printing run of 8,000 was depleted by July 1979, and it was necessary to reprint an additional 20,000.

The Office handled the production of the 70-page 1978 revision of the Guide for the Care and Use of Laboratory Animals, with the press run for the NIH animal care guide, which has become a standard reference, set at 50,000.

Another major OSHR publication project was the revised edition of NIH Primate Research Centers: A Major Scientific Resource. The publication was completely revised with new text and photos. The co-editors, Jim Augustine and Jerry Gordon, were recognized by the American Medical Writers Association (Mid-Atlantic Chapter) which gave them their 1979 First Place Award for "distinguished medical writing for booklets/brochures for professional audiences."

The NIH Minority (Extramural) Research and Training Programs booklet was also revised by OSHR during the year.

A total of 19 DRR wall plaques were produced and distributed to DRR grantee locations by OSHR.

During the fiscal year, the Office received and processed approximately 79 Freedom of Information requests. This represents a slight increase over last year. Approximately 400 hours of clerical and professional time was spent handling these requests.

The Office received and processed 88 Privacy Act requests, representing also about 400 hours of clerical and professional time.

During the year, one of the OSHR staffers was selected as the DRR Coordinator for the 1978 NIH U.S. Savings Bond Campaign. A series of seven financial seminars was conducted by the OSHR staffer in which the entire savings and investment spectrum was carefully discussed. DRR ended up with the third highest percentage of new U.S. Bond employee participation for the year.

The number of publications distributed by OSHR continued to rise. A total of 34,822 publications were distributed through the Office during the year. The Office received 14,677 individual mail requests; 350 individual telephone requests, including Congressional; and 70 individual walk-in requests. Other distribution was made by bulk mail requests and at the NIH Visitors Center.

Office of Administrative Management

The Office of Administrative Management, Division of Research Resources, plans, implements, and evaluates administrative and management services and support to the programs and activities of the Division of Research Resources, and, specifically, provides budgetary support and personnel management, services, and advice; plans and operates the Division of Research Resources data system; provides staff support in planning, evaluation, legislation, and analysis; and participates in special projects, analyses, and studies. The Office of Administrative Management comprises the Special Assistant for Management Planning and Evaluation and the staffs of four Sections--Financial Management, Personnel Management, Administrative Operations, and Data Management--who carry out this mission and report to the Executive Officer, Division of Research Resources.

We concentrated our efforts this year in five areas: program performance evaluations of the Division's programs; automating parts of our budget formulation and justification processes; acting on the Division's Affirmative Action Plan; exercising increased control over direct operations and program management funds; and redesigning the Division's computer-based information system.

PROGRAM EVALUATION

This year, the Department required that the Division of Research Resources develop plans to evaluate the impact of all its programs. In addition to becoming acquainted with the DHEW and NIH program evaluation personnel and policies, we began to explain evaluation, and the Department's policies in that area, to the Division's Program Directors and other senior staff. These training activities will receive greater attention next year as specific evaluation plans and schedules are developed for each program.

We began collaborating with the Program Directors to modify, as necessary, their objectives as developed for the Division's Five-Year Plan so that these objectives can be used to develop indicators of program performance. This work will enable us to propose evaluability assessments in the Fiscal Year 1981 Evaluation Plan, or sooner if sufficient progress is made in one or more programs.

FINANCIAL MANAGEMENT

The Financial Management Section staff formulate, present, and execute the Division of Research Resources budget. Specifically, this Section prepares budget request documents, including schedules and narrative justifications; provides funding and position control data; prepares financial reports required by the Division of Research Resources, NIH, Office of Management and Budget, and the Congress; provides guidance and technical assistance for management of each of the Division's programs; and reviews and analyzes program financial operations.

The accomplishments of this Section were:

- The methods used to forecast the Division's direct operations and program management funding requirements were refined and modified. Accurate forecasting is essential to ensure adequate funding allowances for direct

operations and program management while simultaneously permitting as much funding as possible for awards to be made by the Division's programs. Careful analyses of projected needs such as personal services and benefits, consultant services, travel, automatic data processing, etc., were made by the Financial Management staff after conferring several times during the year with the Division's Program Directors, the Executive Officer, and the Administrative Officer. Precise projections complemented by close monitoring of the Division's funds by the Financial Management staff throughout the year, making adjustments as necessary through reprogramming the Division's programs, refined our control of direct operations and program management funds. This increased control keeps operating expenses to a minimum, thus making available the maximum amount of funds for awards.

- Closer interaction between the Financial Management Section and the Data Management Section fostered a broader knowledge of data--what is needed, what is available, what can be provided, etc. One benefit resulting from this closer interaction was an end-of-year grants and contracts report designed by the Data Management staff in response to Financial Management needs in preparing budget submissions and budget request documents as well as projecting future funding requirements of the Division's programs.

- Parts of our budget formulation and justification processes were automated. This facilitated more rapid retrieval and updating of data, thus enabling us to better meet the extremely short deadlines frequently imposed upon various financial reports, special budget request documents, and major budget submission revisions. Automation also reduced the amount of overtime required.

PERSONNEL MANAGEMENT

The Personnel Management Section staff advise the Division on all aspects of personnel management; and provide central personnel management services, leadership and planning on personnel policy development, training, recruitment, employee development, and equal employment opportunity. These functions are reflected in this Section's accomplishments, listed below.

The following steps were taken to comply with the Division's Affirmative Action Plan and recruitment plan.

- To increase the number of minorities and women in professional job series and mid- and upper-level supervisory positions, the Personnel Management Section requested the Minority Recruitment Section, NIH, to provide applications for all the Division's professional and supervisory recruitment actions. On all other vacancies the Applicant Referral File, EEO Coordinators for the National Heart, Lung, and Blood Institute, and the National Institute of Child Health and Human Development, as well as the Minority Recruitment Section, NIH, were contacted. The Division filled the following professional and supervisory positions:

  Four Division women moved from clerical and technical positions to professional positions;

One Division woman moved to a supervisory professional position;

Two men were selected for professional positions from the Special Placement Register.

- The Personnel Management Section sent source information to all Program Directors and supervisors about recruiting women and minorities. In addition, the Handbook for Recruitment at Minority Colleges was made available.

- All selection criteria and factors affecting eligibility were carefully reviewed to ensure fairness and reasonableness.

- The Division employed one handicapped person. We contacted rehabilitation centers for information on handicapped persons and their skills to provide recruiting officials with information on potential applicants.

The Personnel Management Section will conduct Career Path Seminars for supervisors to aid them in counseling employees on career objectives. This Section will also help to design intra-office training activities to provide developmental experience to employees. Three-year audits to affirm or correct position classifications are being completed on schedule, and every secretarial and clerical position will be reviewed to assure its proper classification under the new Factor Evaluation System standards.

The Personnel Management Section is acting on several Civil Service Reform Act provisions. Supervisors have been advised on the new performance measures; Senior Executive positions as well as supervisory and management positions have been identified, and Senior Executive actions have been processed. Certain Civil Service Reform policies were sent, and will continue to be sent, to affected Division employees.

ADMINISTRATIVE OPERATIONS

The Administrative Operations Section staff provide the Division of Research Resources with overall management analysis and administrative support services such as procurement, space management, travel, and property accountability. This Section also advises key Division officials on administrative policies and practices.

The following were accomplished in the past year:

- The Administrative Operations Section developed an expenditure plan which identified continuing obligations and planned procurement for each quarter.

- The Administrative Operations Section began using new object classification codes, which identify the purpose of travel, to establish firmer control over travel expenditures. Correct object classification coding ensures correct accounting reports, and accurate projections of future travel needs and ceiling constraints.

- This Section submitted an improved automatic data processing plan to the PHS. This improved quality resulted from greater interaction and sharing of responsibility with the Data Management Section, with a corresponding increase in flow and accuracy of information.

- Because Division staff needs a greater word-processing capability, the rental of a scanner/reader is being considered. This machine would complement our other word processors, thus creating a unit of interacting equipment, and would produce man-hour, and thereby dollar, savings, and increase overall productivity.

DATA MANAGEMENT

The mission of the Data Management Section is twofold. This Section (1) designs, develops, operates, maintains, and modifies the Division's computer-based information systems, which include data related to grants, contracts, and other extramural awards made by the Division of Research Resources, as well as the budget workload and related internal operations; and (2) provides data and information for management controls and Division activities.

During this fiscal year, the Data Management Section, with the assistance of the Division of Computer Research and Technology, continued to improve the performance of the Division's information system. During the Fall of 1978, requirements to be satisfied by the information system were defined, which included the limits caused by resources available to operate a system, the user and performance requirements, and the physical parameters, e.g., the number of logical files, data elements, and records. Updating and file restructuring frequencies were determined from prior experience. After reviewing several system-design options, it was determined that a single data base management system could not meet all the Division's needs, thus several applications and system packages will be used, with Mark IV as the principal system package.

New equipment was installed, including three new NIH 7000 display terminals (CRTs) and two Datagraphix terminals. These terminals operate more than eight times as fast as the previously used IBM 2741 terminals. Since display terminals do not automatically provide paper copy, two hardcopy printers (terminals) will be attached to the NIH 7000s. Finally, an IBM 3776 printer was installed and is shared with the National Institute on Aging.

Other significant accomplishments of the past year follow:

- The Division of Research Grants system, IMPAC (and soon CRISP), now provides basic grant information to the Division.

- Through collaboration with pertinent Division personnel, reporting requirements were defined and the number of required reports reduced from 44 to 27.

- A new subsystem was established to identify grants and contracts support to users of the Division-funded resources.

- The first version of the Division of Research Resources Information System Users' Guide was written.

Mark IV's interactive on-line query capability will be implemented in early Fiscal Year 1980. Most user requirements will be satisfied by the present system design; however, Mark IV's inherent flexibility and accessibility should provide a reasonable and easily changed information management system over the next several years.

Fiscal Year 1979
Annual Report
Office of Grants and Contracts Management
Division of Research Resources

The Office of Grants and Contracts Management (OGCM) staff continued to play their important role in the review, negotiation, award making, and the administration of the ongoing grant programs, as well as aiding in the administration of contracts that are made by the Division of Contracts and Grants. During FY 1979, grant awards were made to 795 grantees in the amount of $149,926,000 and 28 contracts were made in the amount of $4,630,000. The types, number and amount of grants and contracts awarded during FY 1979 are as follows:

FY 1979

Grants			R & D Contracts		
		(Dollars in Thousands)			
Type	Number	Amount	Type	Number	Amount
1	37	$ 3,635	1	3	$ 898
2	46	19,228	2	5	1,437
3	46	3,036	3	5	653
5	665	124,012	5	15	1,686
7	1	14			
Total	795	$149,926 1/	Total	28	$ 4,630 2/

Again, during FY 1979, there has been a considerable increase in the intra-agency activity for the Minority Biomedical Support program. In FY 1979 there were ten (10) agreements with NIH Institutes and NIMH totaling $4,595,632, compared to seven (7) in FY 1979, and a 32 percent increase in dollar amount over FY 1979. This activity resulted in a large increase in work load for the OGCM staff.

OGCM and the Data Base Management Section of the DRR Office of Administrative Management during the past fiscal year worked closely together in setting up computerized systems that will furnish information, i.e., commitment base listing, approved/unfunded grants pay lists, and an MBS intra-agency subproject listing. It is expected that the above and other date information will be available early in FY 1980. The Data Base Management Section continued to provide personnel support to enter budget and progress report

1/ Includes $4,946,000 in other than DRR appropriated funds.

2/ Includes $1,174,000 in other than DRR appropriated funds.

information into the data information system. If personnel are available, it is planned in FY 1980 that OGCM will provide the input into the data base. The necessary terminals will be placed in OGCM.

During FY 1979, OGCM personnel assigned to the Animal and Biotechnology Resources programs were put under one supervisor, thereby eliminating one OGCM position to be used elsewhere within the Division. A new Grants Management Specialist supervisor was assigned to the General Clinical Resource Centers program. After almost completing her training, the Stride encumbent transferred to NHLBI, thus delaying plans for filling a vacancy in the future brought about by retirement.

OGCM staff participated in the Grants Management Advisory Committee Workshop, the NIH Grants Management seminar at Duke, the annual Minority Biomedical Support symposium at Atlanta, the workshop for the new Administrative Coordinators at General Clinical Research Centers, and the Biomedical Research Support Grant program directors' meetings at Boston, San Francisco and Los Angeles.

OGCM completed its physical moves and purchased a new filing system which freed up considerable space. Permission was obtained to send grant files to the Records Center after the end of a project period rather than holding until grant was completely closed out, thereby giving us additional space. Since many DRR resource grants have been ongoing for over twenty years, filing of grant folders has become a major problem.

Fiscal Year 1979 Annual Report
Animal Resources Program Branch
Division of Research Resources

INTRODUCTION

The overall objective of the Animal Resources Program Branch (ARB) is to support resource projects that provide, or enable biomedical scientists to use effectively, animals in human health related research. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The Branch objectives are accomplished through a Primate Research Centers Program and a Laboratory Animal Sciences Program.

PRIMATE RESEARCH CENTERS PROGRAM

The seven Primate Research Centers (PRC's) which comprise this program were established with NIH funds during the period of 1961-1965. The Centers and their respective locations are: Washington PRC, Seattle, Washington; Oregon PRC, Beaverton, Oregon; California PRC, Davis, California; Delta PRC, Covington, Louisiana; Yerkes PRC, Atlanta, Georgia; New England PRC, Southborough, Massachusetts; and Wisconsin PRC, Madison, Wisconsin. Each of these Centers is affiliated with a host academic institution. The Centers have unique resources and research environments which are suitable for a broad range of biomedical research areas. The Animal Resources Branch provides core operational support for the Centers through resource grants. Research projects at the Centers are funded largely by NIH categorical institutes, other federal agencies and private foundations through grants and contracts which are held by core staff and collaborative/affiliated scientists. Through their use of nonhuman primate models, these scientists have made many important contributions to biomedical research. During the past year, investigations have been carried out in numerous areas, including reproductive biology, infectious diseases, behavioral sciences, neurosciences, toxicology, nutritional and metabolic diseases and environmental health.

Core support in the amount of $15.242 million provided by this Program in Fiscal Year 1979 has enabled the 145 core staff doctoral-level scientists to conduct research in the Center facilities on 214 projects. These research projects were funded by approximately $3.9 million from 103 NIH research grant/contract awards and $1.5 million from other federal and nonfederal agencies. In addition, the resources and services of the seven Centers were made available to 504 collaborative and affiliated scientists from various academic institutions who conducted research on 136 projects supported by $3.7 million from NIH grants and contracts and $0.7 million from other sources. The Centers also provided research training environments for 215 graduate students engaged in thesis-related research, as well as for 33 visiting scientists. The Program provided salary support for 675 doctoral level, technical and administrative staff personnel.

On a regional basis, the 7 Centers provided a total of over 7,700 biological specimens to 328 scientists. As one measure of their continued scientific productivity, over 900 journal articles and books were published during the past year by the core staff and affiliated/collaborative scientists within the 7 Centers.

The restricted supplies of nonhuman primates available from their countries of origin has continued to cause special emphasis to be placed on domestic breeding of those primate species which are most widely used in the research programs of the Centers. Approximately 1,700 infants and fetuses were produced by the Centers during the past year, representing 60-65 percent of their actual requirements. Small nuclear colonies of a number of less commonly used species were also maintained to assure their survival for future research needs.

The major research themes of each Center and selected examples of research activities during the past year are as follows:

WASHINGTON PRIMATE RESEARCH CENTER, UNIVERSITY OF WASHINGTON AT SEATTLE

The basic research themes of the Washington Center cover the areas of neurological sciences, cardiovascular function, developmental biology, disease models, endocrinology and metabolism and craniofacial structure and function. An extensive collaborative program involved over 60 scientists engaged in a variety of investigative areas. An example of these research activities at the Washington Center is as follows:

Study On Hyaline Membrane Disease

The overall goal of this project is to determine the basic causes and pathophysiology of hyaline membrane disease (HMD) which affects human infants. Macaca nemestrina, which were prematurely delivered by Caesarian section, are used as the animal model (homologue) for these studies. Previous studies at the Washington Primate Research Center have shown that a large proporation (2/3) of the animals prematurely delivered by Caesarian section at approximately 137 days gestation will develop HMD complications that are comparable in their clinical radiologic and pathological features to those observed in human infants. The infant monkeys with HMD demonstrate a decrease in surface active phospholipids in lung tissue and lung wash by 3 hours of age, with no further decrease by 6 hours of age. There is extensive damage of type II epithelial cells, endothelial cells, and bronchiolar epithelial cells, as well as a reduction in lung volume and pressure volume stability. Further studies have attempted to elucidate whether HMD is due to a defect in synthesis of surface active material (SAM) in the type II pneumocyte, a decrease in tissue stores of SAM, or a decrease in secretion of SAM onto the alveolar surface of the lung.

During the past year, various types of analyses have been performed on lung tissue from 18 infant monkeys. No measurable differences were found between

diseased and control animals in the uptake, synthesis or release of surface active phospholipids. Electron microscopic (EM) studies were made on the right upper lung lobe of 10 animals to determine if there was a reduction in the number of type II cells per alveolus in HMD compared to air-breathing controls and to compare the ratios of various cell types within the alveolus (air sac). Preliminary analysis indicates that control animals have a higher number of differentiated type II cells in relation to undifferentiated cells and type I cells, and more lamellar bodies per type II cell than do the lungs of the animals with HMD. The pulmonary parenchyma in HMD has a statistically significant decrease in air/tissue ratio between 3 and 6 hours, indicating that structural changes in the alveolar septum occur in this disease. These studies, including additional work to determine the nature of sequential alveolar collapse in infant monkeys with HMD, are continuing.

OREGON PRIMATE RESEARCH CENTER, UNIVERSITY OF OREGON HEALTH SCIENCES CENTER

Areas of research emphasis at the Oregon Center include reproductive biology, perinatal physiology, cardiovascular pathology, cutaneous biology, immunology, nutrition and metabolic diseases and behavior. An example of activities during the past year is as follows:

Spontaneous Diabetes In Macaca nigra

Spontaneous diabetes in the Celebes Ape (Macaca nigra) has been further characterized metabolically and pathologically and relationships have been established between diabetes mellitus and the development of atherosclerosis.

An increase in glucagon is indicative of diabetes in humans. Concentrations of glucagon in Macaca nigra were found to be significantly greater than human values and biochemical studies have been made to identify the nature of this immunoreactivity. A five-fold increase in immunoreactive forms of glucagon (IRG) was found in borderline diabetics vs. non-diabetic animals. This finding is a useful tool for the diagnosis of impending diabetes, since the increase in IRG precedes clinically detectable signs.

By use of various techniques, aortic atherosclerosis has been quantified and correlated with indexes of clinical diabetes in each animal. Greater aortic atherosclerosis was found with increased levels of clinical diabetes. A causal link has also been established between a specific pathologic lesion in the islets of Langerhans of the pancreas and the expression of hormonal and metabolic aberrations which are then followed by the development of secondary complications. Because the events in the islets of Langerhans occur concurrently with the appearance of amyloid and secondary cell malfunctions, and because these events precede the clinical appearance of diabetes; the name "insular amyloidotic diabetes mellitus" has been proposed for this syndrome.

CALIFORNIA PRIMATE RESEARCH CENTER, UNIVERSITY OF CALIFORNIA AT DAVIS

The major research emphasis of the California Center relates to environmental health sciences and infectious diseases. Other areas under investigation include perinatal biology, behavioral biology, respiratory physiology and immunology. An example of research activities during the past year is as follows:

Pulmonary Mechanics of Nonhuman Primates

Physiological studies have been conducted on the following pulmonary physiology areas: (1) control of breathing, (2) lung volumes and static mechanics, (3) pulmonary flow-volume relationships, (4) response of nonhuman primates (rhesus and bonnet macaques) to general anesthetics, and (5) reactivity of the nonhuman primate pulmonary system to inhaled environmental pollutants.

These studies have revealed some new and unique properties of the nonhuman primate respiratory system. One of the most striking features is the relatively stiff chest wall of the nonhuman primates which is associated with a relatively high resting and expiratory lung volume (approximately 65% of the total lung capacity). This is notably different from the human lung. It is also of interest that the nonhuman primate's residual volume is determined by airway closure, despite their stiff chest wall. The control studies demonstrated that the nonhuman primate uses two strategies to breathe, one similar to man's and the other unlike that of man's. Studies are continuing to further define the basic mechanisms underlying normal respiration in nonhuman primates and to clarify their responses to low-level air pollutants.

DELTA PRIMATE RESEARCH CENTER, TULANE UNIVERSITY

The Delta Center's research programs cover the areas of infectious diseases (a major focus), as well as the areas of immunology, parasitology, biochemistry, neurobiology and urology. An example of their research accomplishments during the past year is as follows:

Prenatal Irradiation Effects On Primate Brain

The objectives of this investigation are to determine the effects of prenatal (in utero) Cobalt-60 irradiation on postnatal development of the nervous, endocrine and immune systems of squirrel monkey offspring. Behavioral, neurochemical, morphological and immunological studies were conducted on animals in four groups: Sham-irradiated control, 10, 100 and 200 rads (R). The results are summarized as follows:

Behavioral tests showed that prenatal irradiation (100 R) caused significant deficits in postnatal visual discrimination at 90 and 365 days after birth, but not at 730 days in squirrel monkey offspring. Adverse effects on reversal of original learning were highly significant at 90, 365 and 730 days after birth. These effects were also related to significant effects on motivation, orientation, hyperactivity and motor performance. Additional

studies are now in progress to establish low-dose (10 R) threshold effects on behavior and to determine if these effects persist from infancy to maturity.

Neurochemical Studies: Morphometric examinations and chemical analyses have been performed on brain tissue of infants (30 days, 1 year and 2 years after birth) that had been irradiated prenatally. The visual, somatosensory, motor, auditory and frontal cortical areas have been analyzed for various enzymes, while relevant chemical assays were performed on midbrain tissue of these animals. These data are currently being evaluated.

Morphological studies showed that neuron and glial cell packing densities were significantly lower in irradiated than control animals. Dendritic spine densities in the giant cells of Meynert of the visual cortex were significantly lower in irradiated than control animals. The neuron population and dendritic spine densities in the hippocampus were markedly decreased in irradiated animals.

Immunology studies demonstrated that prenatal irradiation at 100 R resulted in decreased percentages of blood lymphocytes with surface IgM and decreased blastogenic responses to pokeweed nitrogen (PWM) by lymphocytes from blood, spleen and lymph nodes. These effects were not apparent in irradiated animals at 30 days to 7 weeks age, but were observed in animals 14 weeks to 1 or 2 years of age. These results indicate a deficiency of B-lymphocytes in the animals that were irradiated prenatally at 100 R.

YERKES PRIMATE RESEARCH CENTER, EMORY UNIVERSITY

Research at the Yerkes Center includes psychobiology of great apes and monkeys, anatomical and physiological aspects of the central nervous system, muscle pathology, reproductive biology, immunology and language acquisition. An example of their activities during the past year is as follows:

Immunological Aspects of Malignant Melanoma:

Malignant melanoma tumors of humans spread rapidly and are frequenty fatal. Investigations at the Yerkes Center have used hyperimmunized chimpanzees and monkeys to produce antisera and antibodies to human melanoma cancer cells. Since man and the great apes share certain tissue alloantigens and certain cross-reacting species antigens, the chimpanzee renders a more specific antibody than is obtainable from other experimental animals. After absorption with normal cells from the tumor donor, both the chimpanzee and monkey antibodies were specifically toxic to human melanoma tumor cells. To date, this antisera has been used successfully in immunofluoresence, immunoprecipitation, and radioautography studies. The antibody has been radiolabeled without significant loss of activity.

Investigations are now proceeding in use of the antibody to clarify the nature of the human immune response to this malignant tumor. The antibody has been used successfully in identifying undifferentiated tissue as melanoma in origin. Human melanoma tumors have been grown in athymic mice and it was demonstrated that the antibody administered to the mouse

specifically goes to the tumor. With further development, these findings may permit specific radioscanning for tumor localization and tumor diagnosis.

Studies are currently underway to further refine these techniques, as well as to develop a radioimmunoassay for immunodiagnostic purposes for this human malignancy. Thus, serological diagnosis, radioscanning localization and radioimmunodiagnosis will be the obvious clinical applications from this research effort.

NEW ENGLAND PRIMATE RESEARCH CENTER, (HARVARD UNIVERSITY), SOUTHBOROUGH, MASSACHUSETTS

The New England Center's core research program covers the areas of infectious diseases, psychobiology, pathobiology, viral oncology and diseases of primates. The Center's extensive collaborative research program includes numerous other biomedical areas of investigation. An example of research conducted in the collaborative program at the New England Center during the past year is as follows:

Development Of Erythropoiesis In The Primate Fetus

A study of the response of the nonhuman primate fetus (Macaca mulatta) to blood loss anemia was advanced by the completion of several experiments. For the first time, fetal erythropoietic response was quantitatively measured by a technique involving red blood cell incorporation of 59Fe. On the basis of 59Fe uptake at 24 hours, these studies demonstrated elevated erythropoietic activity in 25 to 30 percent of the anemic fetuses, as compared to data from control animals. In addition to reticulocyte counts, this technique provides another means for quantifying fetal erythropoietic responses in this condition.

A related collaborative project has been initiated to elucidate the factors which control the change during late pregnancy from fetal (L chain) to adult (B chain) hemoglobin. Modified laboratory techniques have demonstrated a progressive change-over from fetal to adult type hemoglobin with advancing gestation. This change-over is more rapid in the nonhuman primate than in the human and is nearly complete at the time of birth. In tissue culture, fetal cells from blood and bone marrow developed colonies more rapidly than equivalent adult cells. Fetal cell colonies developed without exogenous erythropoietin, whereas adult erythroid colonies did not develop in the absence of erythropoietin.

WISCONSIN PRIMATE RESEARCH CENTER, UNIVERSITY OF WISCONSIN AT MADISON

Focused areas of research at the Wisconsin Center include endocrinology, behavior, neuroscience, reproduction and pathology of environmental pollutants. An example of research performed during the past year is as follows:

Studies On Maternal Behavioral Relationships with Infants

Two distinct social behavior studies dealing with maternal-infant relationships were initiated at the Wisconsin Center. The first study concerns the maternal relationship that has developed between a nonhuman primate mother and her youngest infant. As in humans, it can be assumed that this particular relationship may be affected by the birth of a new infant, if only due to the fact that the mother has less time to devote to her previous infant. A group of 54 rhesus monkeys (Macaca mulatta) which have been housed together at the Center since their original capture as a natural social troop are being examined in the study. The objective of this work is to determine whether this change influences the quality and frequency of behavioral interactions, especially those affiliative types that can be termed "aunting" or care-giving behaviors, between the infant and members of other classes of individuals of the troop. Observational data are being collected for each 9-12 month old infant approximately 12 weeks before the birth of their sibling. Their social interactions will be compared to those of mothers who are not yet pregnant to establish an association between the behaviors of mothers and infants. The study is being continued.

The second project, also with rhesus monkeys, is a systematic study of variables concerning the maternal adoption of young infant primates by females other than their biological mothers. Preliminary observations have been used to develop behavioral criteria which define complete adoption in females that have not lived with infants for at least 6 months. Whether the maternal behavior displayed by these non-mothers corresponds to that shown by natural mothers with their own infants remains under study. Results thus far have shown that approximately 80% of the adult multiparous females (who themselves were reared under natural field conditions) immediately adopted 2-12 day old infants that were presented to them. However, the adult, laboratory-reared, multiparous females have not adopted even when an infant is presented to them for one hour each day for 10 days. The ovarian hormonal condition of multiparous females does not appear to affect the probability of adoption occurring under these testing conditions, since 80% of the multiparous females will adopt regardless of whether they are intact, ovariectomized or post-menopausal. Other factors that are still to be investigated include the effects of parity and rearing on adoption.

OTHER PRIMATE RESOURCES

In addition to the Primate Research Centers, the Animal Resources Program Branch supports other primate resource activities. These are as follows:

CARIBBEAN PRIMATE CENTER

This primate resource includes a basic primate colony on the Puerto Rican mainland and semi-free ranging primate colonies on islands off the coast of Puerto Rico. The Center is a valuable resource for research on primate social behavior and is an important breeding center. The Bureau of Biologics, FDA; the National Institute of Neurological and

Communicative Disorders and Stroke; and the Animal Resources Branch all have primate production projects at this Center.

PRIMATE SUPPLY

The Animal Resources Branch at the end of the fiscal year will have six contracts and five grants for the domestic breeding of nonhuman primates. In addition, there is a contract for a Primate Supply Information Clearinghouse. These projects are part of the effort to assure a supply of primates for essential biomedical activities in the face of drastically curtailed importation of wild caught animals. During fiscal 1979 the supply of rhesus monkeys became even more critical because Bangladesh stopped the export of all nonhuman primates. With the loss of this source of animals, practically no rhesus monkeys are being imported. At one time, rhesus monkeys were the most popular research primate.

The contracts are for production of animals for general distribution to NIH extramural investigators. The overall goal of these projects is to provide 1,200 rhesus monkeys, 150 cynomolgus monkeys and 400 squirrel monkeys per year. Each of the contract supported projects is supposed to attain their goal at different dates over the next three years. The squirrel monkey breeding projects will not meet their goals because of difficulty in obtaining breeding stock, losses due to disease, and lower than anticipated reproductive rates. The rhesus and cynomolgus monkey breeding projects will probably come close to meeting their goals. In FY 79, 348 rhesus monkeys, 81 squirrel monkeys, and 22 cynomolgus monkeys have been allocated to NIH extramural investigators from these projects. In addition, 200 rhesus monkeys were provided to Lederle Laboratories at the request of the Food and Drug Administration for safety testing of polio vaccine.

The grant-supported primate breeding projects are for the research and development of breeding techniques as well as the establishment of specialized production colonies. One project was for breeding the endangered species Saguinus oedipus (cotton-topped marmoset), one for developing owl monkey production, one for baboon production, and two projects are to develop production of several species of marmosets.

The Primate Supply Information Clearinghouse is designed to facilitate maximum research utilization of primates already in this country. It functions to match requests for primates, primate tissues and related services with investigators and breeding colonies who have these items available. It provides a means by which primates that have been utilized in a research project, but are no longer needed, can be directed to another research project. During the first 18 months of its operation, a total of 4,242 primates were placed; and cadavers, blood samples and tissues were obtained for 177 projects.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants and contracts. Program areas include support for animal colonies of unusual and special value for research; studies directed at finding animal models which are needed for research on human diseases; projects to assist institutions to comply with the legal and policy requirements for care of laboratory animals; laboratories for the diagnosis and control of diseases of laboratory animals; research related to improving health care and determining environmental requirements of animals used in research; and research training of specialists in the field of laboratory animal medicine. The Program awarded funds totaling $6.365 million in fiscal year 1979, which supported 62 discrete animal research and resource projects, eight institutional training programs, and one individual fellowship award.

ANIMAL MODELS AND SPECIAL COLONIES

The major objectives of this program area are (1) to define, characterize and exploit the relevant biological attributes of selected animals which display potential for use in several areas of biomedical research, (2) to establish, improve or expand special colonies of well characterized animals which are of proven value for biomedical research, but which are not generally available from other sources; and (3) to preserve unique and valuable stocks and strains of animals which might otherwise be lost.

Support for projects related to the establishment of special animal colonies and animal model development remained at approximately the previous year's level; i.e., FY 1978 - $2.257 million (34% of LASP budget) vs. FY 1979 - $1.832 million (29% of LASP budget). A total of 17 projects received support including two new resource grants and 10 ongoing contracts. This latter group of contracts resulted from 3 requests for proposals (RFP) issued in FY 1978. Two RFP's dealt with animal models and were intended to provide pilot support for initial characterization and definition of areas of research utility. One RFP was aimed at providing short-term support to preserve unique and valuable colonies of research animals. It was subsequently decided not to repeat these contract solicitations until the ultimate value of this approach could be demonstrated. At this point, progress reports from the animal model group indicate substantial early progress toward the objectives of each project. The projects encompass a broad spectrum of models as indicated by the following examples: neuronal aging in the vomeronasal organ of garter snakes, the squirrel monkey as a model for the effects of noise on hearing, hereditary canine spinal muscular atrophy in Brittany spaniels, and an animal model for the Guillain-Barre syndrome. The three colonies being supported under the special colony RFP are still intact, but there has been relatively little progress in obtaining stable long-range funding.

Two new grant supported resources were started in FY 1979. One at Michigan State University (MSU) involves a multidisciplinary effort to identify, characterize, and make available new animal models of human genetic diseases. Input regarding potential models will be sought from a variety of sources, including the animal clinics at MSU, veterinary practitioners, and breeding associations and clubs. This general approach has been successful in other settings as represented by three currently supported resources at Washington State University, the University of Alabama at Birmingham, and Bowman Gray School of Medicine. Other animal model projects are oriented around selected species which have potential utility as models in more than one categorical area. The second new grant award to develop techniques for culturing the sea hare, Aplysia californica, is representative of this type of activity. The sea hare is a well established model for neurophysiological and behavioral research. Declining natural populations and problems of maintaining this species have limited research utilization in the past. Development of mariculture and maintenance techniques could favor laboratory breeding over procurement from the ocean and lead to a continuous source of species wherever they were required.

Other grant related activities are primarily related to vertebrate animals including a rabbit inbred and mutant stock resource at the Jackson Laboratory; a mouse mutant gene resource also at the Jackson Laboratory; a congenic mouse resource at Sloan-Kettering Institute; and hamster resources at the University of Texas, Dallas, and Bio-Research Institute, Cambridge, Massachusetts. These and similar projects combine the maintenance and production of special strains or stocks of animals with ongoing research to further development and characterization of the models.

RESOURCE LABORATORIES

The objectives of these laboratories are to provide for improved animal health programs through investigation of naturally occurring disease and related laboratory animal problems, to support studies resulting in new information on diseases of laboratory animals and their etiology, to aid in the elucidation of new laboratory animal models of human disease, and to develop resources including tissues, slides, photographs, etc., for research and training. Most resource laboratories are institutional in nature; however, in some instances it may be desirable and feasible to serve more than one institution in a metropolitan or regional area. There are 15 programs which are currently being supported. One new laboratory was funded during FY 1979.

Resource laboratories have been a major program activity for over 10 years. There has been a continuing turnover in the institutions receiving such awards (support has been terminated for 11 laboratories). The total number has remained relatively constant (13-15) in recent years and approximately 20% of the budget is awarded in this area. Since resources and trained personnel are limited, laboratories have been limited to those settings with at least several million dollars of NIH supported research involving the use of laboratory animals. The

Animal Resources Review Committee reviewed this program area in detail during the past year, particularly regarding the issues of long term support and review criteria for research. Their recommendations were incorporated into an administrative document for applicants which spells out policy requirements and application procedures. This effort should be of considerable value in conducting future reviews and managing this program area.

Laboratory activities encompass a broad spectrum ranging from surveillance and monitoring to conduct of research on important laboratory animal disease problems. The laboratories have been productive in terms of new information and techniques. It is apparent that a multidisciplinary approach to disease problems is necessary in order to identify and isolate etiologic agents and then take appropriate steps to eliminate or control the problem. The interaction of clinicians, virologists, and pathologists was well illustrated by one resource when faced with high death losses in mouse pups born to several large groups of mice. Histologic examination revealed severe inflammation of the cecum and colon, and coronavirus antigen was detected by staining with fluoresceinated antiviral antibody. Electron microscopy revealed viral particles compatible with mouse hepatitis virus (MHV). Subsequent viral isolation was followed by experimental reproduction of the naturally occurring syndrome and reisolation of the virus. The source of infection was traced to contamination of biological material inoculated into mice in a nearby room by a scientist testing for an unrelated agent. This injected material, obtained from insects caught in local forests, was subsequently shown to contain MHV-like virus. The outbreak was controlled by depopulating and disinfecting all infected rooms and laboratories. The influence, sometimes unrecognized, of naturally occurring laboratory animal diseases on research results was particularly well illustrated at another laboratory. During a series of experiments involving the transplantation of skin across a minor histocompatibility region of the mouse, it was noted that unexpectedly prolonged graft survival was occurring in some of these skin graft recipients. Other animals were rejecting their grafts much more rapidly than expected, and still other animals died unexpectedly during the course of the experiment. The problems were presented to the resource laboratory, and an investigation revealed that most of the animals in the experiment were afflicted with Sendai virus. It was decided to investigate this problem to determine whether the Sendai virus and the unexpected results of the experiment were related. Mice free of Sendai virus were obtained, and a barrier facility was set up to prevent accidental contamination. A series of experiments was carried out to compare transplants between infected and noninfected mice. Some infected mice rejected grafts early, especially if the donor of the graft was also infected. Once the acute rejection phase had passed, those animals that failed to reject accepted their grafts for a prolonged period of time, much longer than normal. It was clearly established that intercurrent Sendai virus infections profoundly alter the results of skin transplant experiments across minor histocompatibility regions in mice. Since the mouse is an important experimental tool in the study of basic cellular

immunology, it is anticipated that these results will have a profound effect on the type of mice now deemed acceptable for use in fundamental immunologic studies. These results should markedly improve the reproducibility and value of studies in mice in which various forms of immunity are investigated by the technique of skin transplantation.

Pilot research to further characterize disease processes presented as problems to the laboratory is supported at all the laboratories. Representative of this activity are studies by two groups to isolate the etiologic agent responsible for transmissible ileal hyperplasia (TIH) in hamsters. This disease is considered by many to be the most important infectious disease of hamsters and has potential as a model for chronic inflammatory disease of the small intestine. The morphologic aspects have been well characterized but ongoing efforts have focused on identifying the causative agent. Conventional microbiologic techniques have been unsuccessful, but recent pilot work in one laboratory suggests the organism can be isolated by inoculating intestinal lining cells from infected hamsters into tissue culture cells of various types. The next step is to determine growth requirements and determine if TIH can be induced after inoculation back into hamsters. Additional funding to continue these studies will be sought, using the preliminary data supported by the resource grant. Recognition of potential animal models is an important aspect of working up problems presented to the laboratory. Recently one laboratory received a litter of rats because 4 of the 14 weanling pups had signs of neurological disease (spastic rigidity of the limbs and lack of motor control of the head). The affected rats were sacrificed for histopathological evaluation and the dam and asymptomatic rats were retained for breeding. Test matings produced additional rats with typical neurologic signs in two of three litters. Additional siblings of affected rats were secured from the commercial source to provide an adequate nucleus of breeding stock to perpetuate the disease. At this point, it appears to be an inherited disease (probably autosomal recessive) involving the vestibular system. While many neurological mutants have been described in mice, no inherited neurological disease has been reported in the rat. Thus, this discovery could be of considerable utility since the rat is commonly used for neurophysiological, neuropharmacological, and behavioral research.

RESOURCE RELATED RESEARCH

The Program has provided support to a relatively small number of discrete research projects over the past years. This activity may be summarized as follows:

	FY 75	FY 76	FY 77	FY 78	FY 79
Number of Projects	9	10	13	10	10
Awarded (in thousands)	490	462	607	457	508
Percentage of Total $	8%	8%	10%	7%	8%

Projects falling into this category generally have one of the following objectives: (1) to investigate the etiology, pathogenesis and control of laboratory animal disease problems, and (2) to determine environmental requirements of laboratory animals. For example, currently active projects include the diagnosis and control of mammalian encephalitozoonosis, developing diagnostic/control methods for canine brucellosis, updating nutrient requirements for rats, and control of respiratory mycoplasmosis in rodents. In addition, three ongoing projects are focused on population studies of nonhuman primates in countries of origin. These include census studies of rhesus monkeys in northern India, the relationship of nutrition to social behavior and utilization of living space of baboons in South Africa, and important habitat features relative to West African rain forest primates. Projects of this type are expected to provide data bearing on the conservation of monkeys in their native habitat and their future availability for biomedical research.

Support of resource related research has been accorded a very high priority by the Animal Resources Review Committee. There is widespread recognition among laboratory animal specialists and to a lesser extent among investigators using animals that naturally occurring laboratory animal diseases and environmental factors can have a significant effect on research projects. There are deficiencies in the current state of knowledge relative to many diseases, their recognition, control, etc. In recognition of the need to encourage additional research, the Committee carried out a survey in the fall of 1978 which identified a number of unresolved laboratory animal disease problems. As a next step in stimulating additional targeted research proposals, it was decided to hold several workshops dealing with selected problems in turn. The first workshop on pasteurellosis in rabbits was held March 1, 1979. It was aimed at defining the current state of the art and identification of needs and opportunities. Preliminary indications are that this approach will be successful in stimulating relevant proposals. Thus, it is anticipated that over the next several years; there will be a steady increase in the number of research projects dealing with identified priority areas.

REFERENCE CENTERS AND INFORMATION PROJECTS

The Program supports several reference centers and information projects. These include the Registry of Comparative Pathology located at the Armed Forces Institute of Pathology (consultation, publications, training and research focused on comparative pathology), a Blood Group Reference Laboratory at New York University School of Medicine (nonhuman primate blood typing), an Animal Model Reference Center at Texas A&M-Houston (sperm bank for animal models), and publication of the Laboratory Primate Newsletter. The range of activities encompassed by projects of this type is reflected by the following examples:

1. The Simian Virus Reference Laboratory at the Southwest Foundation for Research and Education, San Antonio, Texas.

The primary purposes of this laboratory are to (1) provide definitive virus diagnostic services, including identification and characterization of viruses that may be present in primate tissues; (2) develop and maintain a working repository of simian viruses and prepare reference seed virus and specific antisera to these viruses; (3) provide consultation services and encourage the pooling of information and exchange of organisms among primate centers and other health organizations; and (4) train interested students in virological laboratory procedures associated with primate investigations. During the last reporting period, a total of 4,052 serum specimens, 233 specimens for virus isolation, and 67 viruses for identification were received from 70 institutions. The Laboratory now has a working repository of over 60 virus reference reagents and reference antisera. Workshops have been held periodically for veterinarians and supervisors of nonhuman primate colonies. The topics covered range from collection and handling of specimens and current laboratory diseases to practical applications and discussions on viral diseases of primates.

2. An Immunohematological Reference Center located at Michigan State University. This reference center was established to produce, standardize and unify the resources available that recognize red blood cell groups, histocompatibility antigens, and other immunogenetic markers in the dog. The canine erythrocyte blood group system has been operational for a number of years. Efforts in the past year focused on reagent production for histocompatibility antigens. Collaboration with other investigators by providing reagents and typing services has increased and has been a major commitment of the Center. During the last reporting period, a total of 95 animals were typed for erythrocyte antigens, 75 were characterized for histocompatibility antigens, and 245 ml. of various typing sera were provided to qualified investigators.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Institutional animal resource improvement projects are awarded to help institutions upgrade their animal facilities and develop centralized programs of animal care in support of their biomedical research programs. A major objective is to enable institutions to comply with the Animal Welfare Act and DHEW policies on the care and treatment of animals. Requests of this type usually include animal cages to meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years, after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program. Requests of this

type peaked in FY 1973 following implementation of the Animal Welfare Act of 1970 (P.L. 91-579) and the DHEW policy on animal welfare. Over the past seven years, 89 institutions have received improvement grants with awards totaling approximately $11.5 million. The following figures summarize activities during this period:

	FY 74	FY 75	FY 76	FY 77	FY 78	FY 79
Reviewed	19	21	19	14	21	9
Approved	12	17	9	7	13	7
New Awards	36	19	6	6	3	4
Total Active Projects	46	38	21	13	11	7
$ Awarded (in $1,000's)	3217	2582	1259	1054	793	709
Percentage of Budget	55%	42%	22%	19%	12%	11%

The above chart indicates a relative steady rate of new proposals in recent years. The largest number of program inquiries still touch on this area. The ability to fund new projects of other types and to combat inflationary costs has come largely at the expense of this program area (note steady decrease in $ awarded and percentage of budget). However, it was possible to fund 4 new proposals this year, primarily because requirements for several nonhuman primate contract activities were reduced because of income earned from the sale of animals. The Animal Resources Review Committee accorded this program area its highest priority and recommended an increased proportion of funds be allocated to institutional improvement projects. It is anticipated that data now being prepared for analysis from the "Survey of Laboratory Animal Facilities and Resources" will identify substantial needs for animal care equipment, renovations, and new construction of animal facilities. Thus, it appears that at least the present level of activity should be maintained for the next several years.

TRAINING

Training in laboratory animal medicine is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

There are eight currently active training programs with a total of 29 funded trainee positions. In addition to the institutional programs, one individual postdoctoral fellowship was active at the end of the fiscal year. Since the usual training period takes approximately 2 1/2 years, there are usually 8-10 graduates per year. Currently available figures indicate that 148 trainees and fellows have completed training since the inception of training grants and fellowships in laboratory animal science and medicine. Forty-eight (48) of these are employed by medical schools

and 57 by other academic, research or governmental organizations. The majority (86) are serving as directors or staff members of a vivarium; 49 are engaged in research or are obtaining additional training; and 13 are in public health, private practice or are retired. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

For the past four years, the active training programs and diagnostic resources have been encouraged to employ veterinary students during their summer break. Eleven programs and 28 students participated this past year. Critiques of the students involved were submitted to the Branch and, in turn, distributed to all the program directors. It appears that this work experience is resulting in greater knowledge and interest in the field of laboratory animal medicine by veterinary students. Several former summer students entered formal postdoctoral programs this year and development of a "pool" of such individuals for future postdoctoral training should result in long-term benefits to the field.

ADMINISTRATION

Two areas of administrative activity have received special attention in fiscal year 1979. These areas are program evaluation and long range planning.

Two program evaluation projects were active in FY 1979. One was an evaluation of the Primate Centers Program. This evaluation was recommended by the DRR Mission Study conducted in FY 1976. The Primate Centers Program evaluation considered the number, location, size, research focus, organization, NIH policy guidelines, and general funding levels desirable for Primate Research Centers and other primate resources. The evaluation was conducted by a panel of 9 distinguished scientists and scientist-administrators. Administrative support for the panel was provided by a contractor. The panel visited each of the Primate Research Centers and surveyed other primate resources. Their final report was received early in FY 1979 and has been reviewed by DRR staff, the National Advisory Research Resources Council, and the Director of NIH.

The second evaluation project was a comprehensive survey of laboratory animal facilities and resources. This survey will provide up-to-date information on the status of our nation's animal resources for the conduct of biomedical research. The results will be basic to formulation of animal resource programs over the next decade. The survey was conducted under contract by the Institute of Laboratory Animal Resources, NRC/NAS. The survey questionnaire encompassed the areas of animal resource costs, administration and personnel, facilities and equipment, and animal sources and use. The survey returns are now being analyzed and a final report is expected by December 31, 1979.

The second major administrative activity was drafting of a long range plan for animal resources. This is part of an overall DRR planning effort. The recommendations of the Primate Centers Evaluation Panel mentioned above are serving as an important input to the plan. The plan will propose better research support for primate center core staff, but a reduction in numbers of core staff, closer Primate Center-host institution relationship, increased primate breeding, and increased research and training in laboratory animal medicine, to mention just a few of the plan's elements.

Table I - Primate Research Centers Program Applications - FY 1979

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	-	--	-	--	-	--
Renewal	-	--	-	--	-	--
Supplemental	-	--	-	--	-	--
Continuation	7	16,862,504	7	15,998,739	7	15,259,669
Totals	7	16,862,504	7	15,998,739	7	15,259,669

1/ Direct Costs Only
2/ Includes Indirect Costs ($2,007,599)

Table II - Laboratory Animal Science and Other Primate Resource and Research Grant Applications - FY 1979

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	34	2,884,216	25	1,870,400	9	968,496
Renewal	9	751,876	6	432,709	6	618,568[3]
Supplemental	1	11,960	1	11,960	5	194,465[4]
Continuation	42	4,295,793	42	3,281,977	42	4,584,418
Totals	86	7,943,845	74	5,597,046	62	6,365,947

1/ Direct Costs Only
2/ Includes Indirect Costs ($1,708,240)
3/ Includes 1 Prior Year Approval
4/ Includes 4 Administrative Interim Actions

Table III - National Research Service Awards Program - Institutional - FY 1979

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	1	41,081	-	--	-	--
Renewal	-	--	-	--	-	--
Supplemental	1	31,389	1	31,389	-	--
Continuation	8	678,609	8	617,226	8	498,400
Totals	10	751,079	9	648,615	8	498,400

1/ Direct Costs Only
2/ Includes Indirect Costs ($31,551)

Table IV - National Research Service Awards Program - Individual - FY 1979

Type	Number Received	Number Approved	Number Funded	Amount Funded
New	2	1	-	--
Renewal	-	-	-	--
Supplemental	-	-	-	--
Continuation	2	2	1	16,600
Totals	4	3	1	16,600

Table V - Laboratory Animal Science and Other Primate Resource and Research Grants - Project Type - FY 1979

Type	Number Received	Amount Requested[1/]	Number Approved	Amount Approved[1/]	Number Funded	Amount Funded[2/]
Resource Research	25	1,211,137	17	660,340	10	508,824
Primate Resource	5	499,341	4	220,103	4	335,612
Special Colonies and Models	20	1,915,998	19	1,418,288	17	1,832,883
Basic Improvement	12	1,583,530	11	1,222,914	7	709,143
Diagnostic Labs.	16	1,929,064	15	1,469,041	15	1,951,926[3/]
Animal Reference	7	779,775	7	581,360	8	990,763[4/]
Research Career	1	25,000	1	25,000	1	36,796
Totals	86	7,943,845	74	5,597,046	62	6,365,947

1/ Direct Costs Only
2/ Includes Indirect Costs ($1,708,240)
3/ Includes 4 Administrative Interim Actions
4/ Includes 1 Prior Year Approval

Table VI - Laboratory Animal Science and Other Primate Resource Contracts

	Number Supported	Amount Funded
Special Colonies and Models	10	368,113
Primate Resources	1	474,180
Primate Supply	5	493,519
Program Support	3	159,572
Totals	19	1,495,384

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INTRODUCTION

The Biotechnology Resources Program (BRP) was established in 1962 as the Special Research Resources Branch of the Division of Research Facilities and Resources to provide support for complex technological capabilities required in biomedical research. The Program has an array of diverse resources, all designed to meet one or more specific technological needs of biomedical research scientists.

Emphasis at present is in resources for computer science applications in biomedicine, biomedical engineering and specialized instrumentation for study of biological structure and function which includes mass spectrometry, nuclear magnetic resonance, electron spin resonance, electron microscopy, electron microanalysis, x-ray diffraction, and biomedical kinetics. As new advanced technological tools become pertinent to health research, the Program makes these tools available to the biomedical research community.

Current senior staff members are:

Dr. Suzanne S. Stimler, Director;

Dr. William Roy Baker, Jr., Special Assistant for Biomedical Engineering;

Dr. Charles L. Coulter, Head Biological Structure Section;

Dr. Jack Hahn, Head, Computer Technology Section;

Mr. John White, Office of Grants and Contracts Management, serves as Supervisory Grants Management Specialist and Ms. Delma Ellstrom serves as Grants Management Specialist for the Program.

EXPENDITURES BY CATEGORY

Types of Biotechnology Resources

The Program supported resource grants, resource-related research project grants and contracts during FY 1979. The varied technologies the Biotechnology Resources provide are classified as follows:

Type	Number (Grants & Contr.)	$ Awarded FY 1979
Computer		
Information and Knowledge Systems	8	4,143,672
Computer Science and Technology	10	4,353,151
Biomedical Engineering	2	832,394
Biological Structure and Function		
Mass Spectrometry	6	1,044,383
Nuclear Magnetic Resonance	11	1,207,028
Diffraction	1	339,483
Electron Spin Resonance	1	173,450
Biomedical Kinetics	1	333,056
Electron Microscopy	4	882,303
Electron Microprobe	1	413,540
Cellular and Biochemical Materials	2	521,661

The aggregate annual level for the grant and contract activities is approximately $14.5 million. A list by Program category of BRP-sponsored grants and contracts is given in Table I, together with brief descriptions of the capabilities and research emphasis or applications for each.

Table II gives information on resource grant applications by type and Program category for FY 1979. Numbers of grants submitted, amounts requested, numbers of grants approved, funded, and amounts funded are provided in Table II.

TABLE I

BRP-Funded Grants and Contracts During FY 1979
As of September 1, 1979

Number	Principal Investigator and Institution	Title	Capability	Research Emphasis or Applications	FY 1979 $ Award	Cumulative $ Awards
			Computer Resources			
Information and Knowledge Systems						
5R24-RR612-10	Carl Djerassi, Ph.D. Stanford Univ. Stanford, Ca.	Resource-Related Research: Computers and Chemistry	Computer software for interpretation of mass spectrometry data	Development of techniques for computer-assisted molecular structure elucidation	227,601	2,944,619
5P41-RR-643-08	Saul Amarel, Sc.D. Rutgers Univ. New Brunswick, N.J.	Special Research Resource: Computers in Biomedicine	Access to time-sharing systems	Application of artificial intelligence to clinical decision making and medical modeling	675,986	3,382,041
3P41-RR-785-06S1 5P41-RR-785-07	Edward A. Feigenbaum, Ph.D. Stanford Univ. Stanford, Ca.	S U Medical Experimental Computer Resource	Remote access through computer networks	Biomedical research applications of artificial intelligence and computer sharing for health research	186,375 954,111	5,847,640
5R24-RR-1059-03	Todd Wipke, Ph.D. Univ. of Ca. Santa Cruz, Ca.	Resource-related Research: Biomolecular Synthesis	Application of computers to synthetic organic chemistry	Computerized evaluation of chemical synthesis choices	89,629	280,880
5P41-RR-1096-03	Peter Szolovits, Ph.D. Mass. Inst. of Tech. Cambridge, Mass.	Laboratory for Clinical Decision Making	Computer-based clinical decision systems	Artificial intelligence applications to clinical decision systems	153,814	483,589

5R24-RR-1101-03	Harry E. Pople, Ph.D. University of Pittsburgh Pittsburgh, Pa.	Clinical Decision Systems Research Resource	Computer-based diagnostic consultation systems	Artificial intelligence methodology for clinical decision systems	158,156	562,339
N01-RR-9-2107	ADP Network Services, Inc. Waltham, Mass.	Hardware Maintenance Contract in Support of PROPHET System	PROPHET Timesharing Computer Resource	Chemical/Biological Information Handling	1,010,436	1,010,436
N01-RR-8-2118	Bolt, Beranek and Newman, Inc. Cambridge, Mass.	Software Development Maintenance and Technical Assistance for PROPHET System	PROPHET Timesharing Computer Resource	Chemical/Biological Information Handling	687,564	6,618,454
Computer Science and Technology						
5R24-RR-7-16	Richard A. Robb, Ph.D. Mayo Foundation Rochester, Minn.	Computer Analyses of Biosystem Structures and Functions	Image Processing and Analysis	X-ray, ultrasound and non-invasive monitoring of radionuclide imaging of major organs of the body	341,754	6,599,810
3P41-RR-276-13S2 1/	Ivan R. Neilsen, Ph.D. Loma Linda Univ. Loma Linda, Ca.	Development of Biomedical Computation Facility	Dedicated systems and time-sharing on-line graphics	Biomedical modeling, computer-assisted pulmonary function testing, EKG analysis	178,160	1,995,438
5P41-RR-374-13	Theodore H. Kehl, Ph.D. Univ. of Wash. Seattle, Wash.	Support for Physiology and Biophysics Computer	BASIL computer system	Computer support to on-line control and analysis of physiology and biophysics	262,408	2,328,384
5P41-RR-396-12	Jerome R. Cox, Jr., Sc.D. Wash. Univ. St. Louis, Mo.	A Resource for Biomedical Computing	Dedicated computers and macromodule systems	Information system technology cardiac rhythm monitoring, biomolecular modeling, positron-emission tomography	2,087,389	18,554,783
2P41-RR-442-11	Cyrus Levinthal, Ph.D. Columbia Univ. N.Y., N.Y.	Computer Resource for Image Processing and Displays	Image processing and interactive graphics	Neuro-anatomical modeling, biomolecular modeling	223,910	3,130,657
5P41-RR-757-07	Joseph Kraut, Ph.D. Univ. of Ca. La Jolla, Ca.	Computer Resource for Biomolecular Research	Computer-based automated laboratory systems	Biomolecular modeling, on-line acquisition of x-ray crystallographic data	372,817	1,624,861

3P41-RR-898-05S1 3P41-RR-898-05S2	Frederick Brooks, Ph.D. Univ. of N.C. Chapel Hill, N.C.	Regional Graphics Resource for Molecular Studies	Interactive Computer Graphics	Biomolecular modeling of proteins and nucleic acids	78,823 94,261	672,394
3P41-RR-1081-02S2* 1/	Robert Langridge, Ph.D. School of Pharm., U. Ca. San Francisco, Ca.	Special Research Resources for Biomolecular Graphics	Stand alone medium computer and graphics	Biomolecular modeling	164,237	1,658,422
5P41-RR-1089-03	Robert Schoenfeld D.E.E. Rockefeller Univ. N.Y., N.Y.	A Microprocessor Biotechnology Resource	Application of microprocessor-based instruments to biology	Development of microprocessor-based systems for biological research	109,992	366,264
NO1-RR-8-2107**	Wilfrid J. Dixon, Ph.D. Univ. of Ca. Los Angeles, Ca.	Continued Support of the BMD/BMDP Program	Maintenance, continued development distribution BMD/BMDP statistical packages	Computer packages for biomedical research	439,400	23,807,591
			Biomedical Engineering			
5P41-RR-857-05	Wen H. Ko, Ph.D. Case Western Reserve Univ. Cleveland, Ohio	Biomedical Electronics Resource	Microelectronics fabrication, packaging and evaluation	Micro-electrodes, solid state physical and gaseous sensors, implant telemetry	695,687	2,411,750
5P41-RR-1086-03	James B. Angell, Sc.D. Stanford Univ. Stanford, Ca.	Resource for Silicon Biomedical Tranducers	Microelectronics and micromaching of sensors	Biomedical tranducers for clinical research	136,707	763,805
			Biological Structure and Function			
Mass Spectrometry (MS) Note: GC refers to Gas Chromatography						
2P41-RR-317-13	Klaus Biemann, Ph.D. M.I.T. Cambridge, Mass.	Mass Spectrometry Facility for Biomedical Research	High resolution MS, GC/medium resolution MS	Drug identification, drug metabolism, molecular structure analysis	377,019	2,959,256
5P41-RR-480-11	Charles C. Sweeley, Ph.D. Michigan State Univ. East Lansing, Mich.	Mass Spectrometry Facility	High resolution MS; GC/MS; field desorption MS	Metabolites in biological fluids, structure determination of lipids, analysis of complex mixtures	159,175	1,313,486

5P41-RR-719-05	A.L. Burlingame, Ph.D. Univ. of Ca. Berkeley, Ca.	Bio-Organic Biomedical Mass Spectrometry Resource	GC/low and high resolution MS	Toxic chemical metabolites, urinary organic acids, high resolution MS data from chromatographic effluents	297,267	1,329,015
5P41-RR-862-06	Frank H. Field, Ph.D. Rockefeller Univ. N.Y., N.Y.	A Mass Spectrometric Biotechnology Resource	Low and high resolution MS, GC/chemical ionization quadrupole MS	Fission fragment MS; drug metabolism, drug assays, peptide sequencing	101,454	719,551
5P41-RR-922-03	Heinz G. Boettger, M.S. Ca. Inst. of Tech. Pasadena, Ca.	Mass Spec. Resource for Biomedical Applications	Mass Spectrometry	Multiple ion monitoring	74,454	188,190
3P41-RR-954-03S2 1/	William F. Holmes, Ph.D. Washington Univ. St. Louis, Mo.	A Resource for Biomedical Mass Spectrometry	GC/low resolution MS; chemical ionization	Drug and vitamin metabolism; inborn metabolic errors	35,014	943,733
Nuclear Magnetic Resonance						
5P41-RR-292-14	Aksel A. Bothner-By, Ph.D. Mellon-Pittsburgh Carnegie Corp. Pittsburgh, Pa.	NMR Facility for Biomedical Studies	250 MHz NMR Spectrometer	Structure and function of hemoglobins, biological membranes, proteins	147,847	1,939,673
5P41-RR-542-09	George McDonald, Ph.D. Univ. of Pa. Philadelphia, Pa.	Middle Atlantic Regional NMR Facility	220 MHz, NMR Spectrometer; 360 MHz, NMR Spectrometer	Enzyme/substrate interaction mechanisms; RNA structure	114,378	1,505,511
3P41-RR-574-08S1 1/	David M. Grant, Ph.D. Univ. of Utah Salt Lake City, Utah	Regional Research Facility in NMR	100 MHz NMR spectrometers; 300 MHz NMR spectrometer	^{13}C labelled macromolecules; ^{15}N-^{13}C coupling constants of depeptides	146,406	1,513,868
3P41-RR-639-05S1 1/	Jay A. Glasel, Ph.D. Univ. of Conn. Hartford, Conn.	A New England Area NMR Research Resource	100 MHz NMR spectrometer	Structure and function of Peptides and Hormones	67,037	490,312

5P41-RR-708-05	Nathan O. Kaplan, Ph.D. Univ. of Ca. La Jolla, Ca.	UCSD Resource Facility for NMR and Mass Spectrometry	220 MHz NMR spectrometer; CFT-20 spectrometers; GC/low resolution MS	Structure/function relationships of peptide hormones	145,884	830,981
2P41-RR-711-07	Oleg Jardetzky, M.D. Stanford Univ. Stanford, Ca.	High Frequency NMR Biotechnology Resource	360 MHz NMR spectrometer	Conformational changes on the lac-repressor proteins, membrane immuno chemistry enzyme-substrate complexes	228,784	1,178,043
3P41-RR-798-05S1 1/	James H. Prestegard, Ph.D. Yale Univ. New Haven, Conn.	Southern New England High Field NMR Facility	270 MHz NMR spectrometer	Structure of biological membranes, drug and hormones action, protein structures	31,080	571,738
5P41-RR-892-04	Thomas L. James, Ph.D. Univ. of Ca. San Francisco, Ca.	NMR Spectroscopy Resource	100 MHz NMR spectrometer	Lipid mobility in membranes enzyme mechanisms	53,996	400,982
3P41-RR-995-03S1 2P41-RR-995-04	Leo J. Neuringer, Ph.D. M.I.T. Cambridge, Mass.	A National NMR Facility for Biomedical Research	270 MHz NMR spectrometer; 290 MHz NMR spectrometer for studies of solids	Model membrane systems; lipid-protein interactions	60,006 17,000	603,827
5P41-RR-1039-03	Paul C. Lauturbur, Ph.D. Research Found. of SUNY, L.I., N.Y.	Facility for Biomedical NMR on Radioactive Samples	100 MHz NMR Spectrometer	3_H Labelled Compounds	74,979	252,470
5P41-RR-1077-03	John H. Markley, Ph.D. Purdue Univ. West Lafayette, Ind.	A Regional NMR Resource for Biomolecular Research	360 MHz NMR spectrometer	Macromolecular structure studies	119,631	849,275
Diffraction						
3P41-RR-1135-01S1 5P41-RR-1135-02	Robert H. Kretsinger, Ph.D. Univ. of Va. Charlottesville, Va.	Development of an Area X-ray Diffractometer	A multiwire detector provides the basis for rapid x-ray data collection	Emphasis will be on data collection for protein crystals	82,984 256,499	375,242

Electron Spin Resonance (ESR)						
3P41-RR-1008-03S1 2P41-RR-1008-04	Harold M. Swartz, M.D., Ph.D. Medical College of Wis. Milwaukee, Wis.	Biomedical ESR Spectroscopy Center	ENDOR, ELDOR Pulse ESR Spectrometers	Clinical applications of ESR, structure of free radicals in biological materials, enzyme kinetics; paramagnetic changes during tumor development	168,950 4,500	1,035,554
Biomedical Kinetics						
3P41-RR-886-04S1 5P41-RR-886-05	Edward L. Powers, Ph.D. Univ. of Texas Austin, Texas	Center for Fast Kinetics Research	Electron Pulse 5.5 MeV Van de Graff accelerator for radiolysis studies	Reactions of DNA and OH radicals; dose rate effects in irradiated cells	111,264 221,792	1,091,435
Electron Microscopy						
5P41-RR-570-09	Hans Ris, Ph.D. Univ. of Wis. Madison, Wis.	Electron Microscope Facility for Biomedical Research	1 MeV electron microscope	3-D structure of chromosomes, neuronal tissues, frozen tissues	124,745	1,491,714
5P41-RR-592-10	Keith R. Porter, Ph.D. Univ. of Colo. Boulder, Colo.	High Voltage Electron Microscopy of Biological Systems	1 MeV electron microscope	3-D structure of whole-cultured cells, intracellular systems; isolated mitotic apparatus	319,990	3,359,482
2P41-RR-715-07	Joseph S. Wall, Ph.D. Assoc. Universities, Inc. Upton, New York	Electron Microscope Facility	100 KV scanning transmission electron microscope	Viruses, nucleic acids, membranes	259,907	1,254,725
5P41-RR-984-04	Albert V. Crewe, Ph.D. Univ. of Chicago Chicago, Ill.	Scanning Microscope Laboratory for General Faculty Use	40 KV Scanning Transmission Electron Microscope, Hitachi SEM, Coates-Welter SEM	Atomic resolution of single heavy atoms in biological materials	177,661	850,874

Electron Microprobe						
5P41-RR-679-08	Claude P. Lechene, M.D. Harvard Medical School Boston, Mass.	Biotechnology Resource in Electronprobe Microanalysis	CAMECA electron microanalyzer	Elemental composition of biological tissues	413,540	2,400,293
			Cellular and Biochemical Materials			
3P41-RR-961-03S2	Donald A. Glaser, Ph.D. Univ. of Ca. Berkeley, Ca.	Facility for Automated Experiments in Cell Biology	Large-scale production of mutant cells	Mutants of microbial and animal cell cultures	350,000	4,337,208
5P41-RR-962-04	Nicholas A. Matwiyoff, Ph.D. Univ. of Ca. Los Alamos, N. Mex.	A National Stable Isotope Resource at Los Alamos	Provision of labelled compounds with stable isotopes of C, O, and N for biological research	Syntheses of labelled compounds with stable isotopes	171,661	737,404

* Includes grant support through fifth year of previous grant (2P07-RR-00578-05A1)

** Includes grant support through sixteenth year (2P41-RR-0003-16A1)

1/ Phase-out awards

TABLE II

Biotechnology Resource Grant Applications -- FY 1979

Type	Number Reviewed* FY 79	Amount Requested (Direct)	Number Approved FY 79	Amount Approved (Direct)	Number Funded	Amount Funded		
						Direct	Indirect	Total
Computer								
New	4	2,815,026	2	659,621	0	0	0	0
Renewal	4	1,466,588	4	1,011,711	1	165,024	58,886	223,910
Supplemental (Competing)	1	54,448	1	54,448	0	0	0	0
Supplemental (Interim)	5	557,043	5	557,043	5	557,043	144,813	701,856
Continuation	11	6,715,504	11	4,384,534	11	3,650,530	783,127	5,433,657
Totals	25	11,608,609	23	6,667,357	17	4,372,597	1,986,826	6,359,423
Biomedical Engineering								
New	1	204,478	1	204,478	0	0	0	0
Renewal	0	0	0	0	0	0	0	0
Supplemental (Competing)	0	0	0	0	0	0	0	0
Supplemental (Interim)	0	0	0	0	0	0	0	0
Continuation	2	667,545	2	680,224	2	484,694	347,700	832,394
Totals	3	872,023	3	884,702	2	484,694	347,700	832,394
Biological Structure and Function								
New	12	3,689,468	7	1,804,624	0	0	0	0
Renewal	10	2,118,783	10	1,697,768	5	622,692	264,518	887,210
Supplemental (Competing)	0	0	0	0	0	0	0	0
Supplemental (Interim)	8	496,070	8	479,070	8	479,070	223,671	702,741
Continuation	16	2,387,508	16	1,988,364	16	1,968,648	834,644	2,803,292
Totals	46	8,691,829	41	5,969,826	29	3,070,410	1,322,833	4,393,243

Type	Number Reviewed* FY 79	Amount Requested (Direct)	Number Approved FY 79	Amount Approved (Direct)	Number Funded	Amount Funded		
						Direct	Indirect	Total
Cellular and Biochemical Materials								
New	0	0	0	0	0	0	0	0
Renewal	1	293,251	1	223,103	0	0	0	0
Supplemental (Competing)	0	0	0	0	0	0	0	0
Supplemental (Interim)	2	267,176	1	267,176	2	267,176	82,824	350,000
Continuation	1	866,000	1	121,331	1	115,830	55,831	171,661
Totals	4	1,426,427	3	611,610	3	383,006	138,655	521,661
GRAND TOTALS	78	22,598,888	70	14,133,495	51	8,310,707	3,796,014	12,106,721

*New, Renewal, and Competing Supplemental applications reviewed at September 1978, February 1979 and May 1979 Councils

PROGRAM DEVELOPMENTS

Resource Directory

The Research Resources Directory for Biotechnology Resources continues to be in constant demand. The Directory first issued in May 1977, revised in August 1978, is being revised again in 1979. The latest edition will contain a general description of the resources' technologies and scientific capabilities written in language understandable by scientists not knowledgeable in uses of the specialized technologies offered by the Program.

Exhibit

An exhibit featuring the Resource Directory of biotechnology resources was shown at annual meetings of Federation of Associated Societies in Experimental Biology (FASEB) in April 1979, and Electron Microscopy Society of America and Microbeam Analyses Society in August 1979. The exhibit was well attended at both meetings. Over 500 copies of the Directory were distributed at the FASEB meeting.

Resource Accomplishments

The Research Resources Reporter, published monthly under DRR contract with Tracor Jitco, Inc., contained 14 articles this past year on various facets of the Biotechnology Resource Program-sponsored activities. Research accomplishments were featured in articles on: a bioautofuel cell which transforms energy of biochemical reactions occurring in the body to electricity to power microelectronic implanted devices for blood pressure, EEG and glucose monitoring in the body developed at the Biomedical Electronics Resource, Case Western Reserve University (May 1979); a dynamic spacial reconstructor imaging device for real time displays in three dimensions of the heart, lungs and circulatory system developed at the Mayo Foundation (January 1979); a new technique for medical imaging, zeugmatography, which uses a magnetic field and radio waves to produce images of internal tissues and organs developed in part at the Facility for Biomedical NMR on Radioactive Samples, SUNY, Long Island, New York (January 1979); use of the Computer Facility for Real Time Data Acquisition and Display at the University of California, San Diego for studying the structure of gene products induced by cancer-causing viruses in rats (March 1979); a computerized genetic counseling system at the M.I.T. Resource for Clinical Decision Making (February 1979); production of the first large volumes of nearly pure Carbon-13 isotope for use in pharmacological research at the National Stable Isotope Resource at Los Alamos (November 1978); detection of Vitamin B-12 deficiency in a six-month old child using the Resource for Mass Spectrometry, University of California, San Diego (April 1979); and confirmation of the structure of fibrinogen, a protein essential to blood clotting, at the Scanning Transmission Electron Microscope Facility, Brookhaven National Laboratories (July 1979). Special articles about capabilities offered at resources were on the Resource for Silcon Biomedical Transducers, Stanford

University and the Biomedical Electronics Resource, Case Western Reserve University (December 1978); Computer Graphics Resource for Molecular Structure Studies, University of North Carolina (March 1979); Regional NMR Resource for Biomolecular Research, Purdue University (January 1979); applications of NMR to biomedical research at the NMR Facility for Biomedical Studies (January 1979); application of mass spectrometry to biomedical research at the Michigan State University Mass Spectrometer Facility (April 1979); and the Scanning Transmission Electron Microscope Resource at Brookhaven National Laboratory (October 1978). A special edition published in September 1979 on the Stanford University Medical Experimental Computer SUMEX-Artificial Intelligence in Medicine (AIM) Resource gave detailed information on the unique capabilities of this resource and the projects being conducted that use the resource. The New York Times in May 22, 1979, reported on a computer model describing the disorder paranoia which was developed in the SUMEX-AIM resource.

Budget

The most serious problem facing the Program is its inability to fund meritorious resource grant applications. The budget in "real" dollars has been level since 1974. When the budget is adjusted for inflation to give constant dollars, the Program's budget has shown a net decrease over the past decade. Budget figures from 1969 to 1979 for the Program are given in Table III. Since 1969 the Program has decreased 40 percent in constant dollars or in its ability to purchase research and equipment. In contrast, the total NIH budget has increased in constant dollars by 47 percent from 1969 to 1979 (Basic Data Relating to the NIH, 1979).

Type 5 applications have higher budgets over the past year's support because of increases in salaries and indirect costs both due to inflation. Type 2 applications have in addition to these increases, requests to replace or update obsolete equipment and increases from higher costs of supplies and equipment maintenance. The Program receives requests for major replacements or updates in most renewal applications because lifetimes for technology to stay at the leading edge of the technology's state-of-art range from 5 to 10 years.

To keep within the BRP FY 1979 budget, it was necessary to phase out six competing renewal resource grants. No new grants were awarded this year. There are 19 approved, unfunded grant applications (Type 1 and Type 3) requesting $5,604,890 from BRP. These will be kept administratively active and considered for funding in 1980.

TABLE III

Past Decade Appropriations
Biotechnology Resources Program (BRP)
Chemical/Biological Information-Handling Program (CBIHP)

Year	BRP in $1,000	CBIHP in $1,000	Total	NIH R&D Price Deflator [a]	Budget in Constant $ in $1,000
1969	11,020	1,050	12,070	100	12,070
1970	11,003	1,050	12,053		
1971	10,007	1,000	11,007		
1972	11,113	1,060	12,173		
1973	11,068	1,005	12,073		
1974	13,406	1,000	14,400		
1975	12,165	1,000	13,165		
1976[b]	12,353	1,000	13,353		
1977	13,013	1,090	14,103		
1978	13,018	1,164	14,182		
1979	13,018	1,164	14,182	195.7	7,247

[a] Basic Data Relating to National Institutes of Health, 1979

[b] Does not include transition quarter funds

Support of NIH Categorical Institutes

One of the primary measures of accomplishment that can be applied to the Biotechnology Resources Program is the extent to which its sponsored resources assist the various NIH categorical programs. With their cadres of highly skilled staff scientists and their specialized and often unique facilities, Biotechnology Resources are frequently the scene of productive encounters between experts in a given technology and experts in a given medical discipline. Table IV gives additional insight into the breadth and depth of this Program on the health research supported by the DHEW.

Table IV lists the number of projects that made use of the Biotechnology Resources and the value of these projects in thousands of dollars of grant support for these projects. The data is presented for the NIH Institutes and some of the other Public Health Service Administrations. The distribution of research assisted by the Biotechnology Program reflects in part how apportionment of research funds to the NIH Institutes and other agencies brings research talent to a given area and how the staff of the Biotechnology Resources respond in meeting these demands.

The data in Table IV was obtained from progress reports submitted in 1978 and analyzed by the Office of Program Analysis, DRR. Similar information was not collected and analyzed using comparable data from 1979 progress reports. However, since there has been little change in the Program the past several years, the data in Table IV gives a good approximation of the usage of Biotechnology Resources by different Institutes in 1978.

TABLE IV

Number and Dollar Amount by NIH Institute and PHS Administrations of Projects Receiving Biotechnology Resource Support From 43 Out of 48 Resources

Active During FY 1977

NIH Institute	Number of Projects	Dollar Value of Projects in $1,000
Allergy and Infectious Diseases	30	1,595
Arthritis, Metabolism and Digestive Diseases	74	6,026
Cancer	148	16,826
Child Health and Human Development	46	6,487
Dental Research	9	346
Environmental Health Sciences	11	1,516
Eye	26	1,974
General Medical Sciences	174	10,595
Heart and Lung	85	10,615
Neurological and Communicative Disorders and Stroke	55	6,177
National Library of Medicine	5	357
Total	663	62,514
Other PHS Administration Components:		
Alcohol, Drug Abuse and Mental Health Administration	65	7,539
Food and Drug Administration	9	424
Health Resources Administration	54	4,372
Grand Total	791	74,849

MEETINGS, WORKSHOPS, CONFERENCES

Biotechnology Resources Review Committee

The Biotechnology Resources Review Committee has developed over the past year a series of reports which set forth needs, opportunities, scientific directions, and priorities for the Program. These reports provide a basis for planning and new initiatives both in the short term through the NIH Forward Plan, and in the long term through the Five-Year Plan. The Committee expects to have presentations from several Resources in the coming year to further educate the Committee on the nature of Biotechnology Resources and on the technical and administrative problems and opportunities which Program Directors face. Committee meetings are held at least twice a year and are open to the public except when confidential materials and prospectuses are being reviewed.

Biomedical Engineering

A Workshop sponsored jointly by the resources in biomedical engineering at Stanford and Case Western Reserve University and the Biotechnology Resources Program was conducted at Stanford University on June 27-29, 1979. This Workshop on Implantable Micro-Transducers and Systems; Packaging Methods and Testing Criteria was designed to examine the problems of long-term reliability of implanted electronic systems. Emphasis was on exchange of information between experts in discovery, development, clinical testing, and quality assurance of implanted microsystems. The goal was to identify problems in reliability, and to define solutions to these problems. A digest of this Workshop is available from Dr. James B. Angell, Department of Electrical Engineering, Stanford University, Stanford, California 94305.

A Workshop on Hearing Loss was held at NIH on August 7-8, 1979, sponsored by NIA, NINCDS, the resource at Case Western Reserve University, and the Biotechnology Resources Program. The first session dealt with the knowledge recently incorporated in what is known about the many manifestations of hearing loss. The second session addressed what can be accomplished through the advances in technology and biomedical engineering that was not available in the past to ameliorate hearing problems.

Artificial Intelligence

Medicine

A small workshop was held May 17-20, 1979, by the Laboratory for Clinical Decision Making, M.I.T. The workshop was concerned with technical computer science issues of the representation of medical knowledge, explanation and justification, knowledge base acquisition and maintenance, and the detailed computational mechanisms in INTERNIST II. Consideration was also given to current and future difficulties of bringing the artificial intelligence in medicine programs to clinical use.

Biochemistry

In December 1978 three, 3-day workshops were held at Stanford University to introduce experts in the field of biomolecular structure elucidation to the first version of the exportable version of CONGEN. CONGEN is a series of interactive computer programs which assists scientists to explore potential structures of unknown compounds. The programs draw structural conclusions from physical and chemical data.

NMR Conference

A Symposium to dedicate the Regional NMR Resource for Biomolecular Research at Purdue University was held November 17-18, 1978. Emphasis was on use of NMR to study glycoproteins, protein dynamics, conformation of mobil peptides, tRNA, biological membranes, and the red blood cell.

CONTRACTS

PROPHET Computer System

A. Introduction

The PROPHET computer system provides the biomedical research community with the most comprehensive set of tools currently available on any single system for data management, graphical and statistical analysis, curve fitting/mathematical and molecular modeling. The computer-naive scientist easily utilizes the system via English language-like commands. Ease of use is facilitated by the availability of (1) extensive and frequently updated manuals; (2) a 24-hour telephone hot line; and (3) an on-line message system. The more computer-sophisticated user can write his own programs in PL-PROPHET, a versatile programming language available on the system. Existing software programs are continually reevaluated and updated. New programs are designed by the software development and user assistance staff at Bolt, Beranek and Newman in response to user needs established through several mechanisms, including frequent visits to each user site, an annual users colloquium, and the PROPHET telephone line.

B. The User Community Served

There are approximately 275 scientists utilizing PROPHET tools at 19 PROPHET user sites. These scientists conduct more than 300 projects supported by over 250 grants from government and private granting agencies.

C. New PROPHET Sites

During FY 1979, three new sites were added to the system:

1. The Chemistry Department at Louisiana State University in Baton Rouge, Louisiana;

2. The Biology Department and other allied sciences at Yale University, New Haven, Connecticut (upgraded from a teletype site);

3. The Wellcome Research Laboratories of the Burroughs Wellcome Company, Research Triangle Park, North Carolina.

D. New PROPHET Tools

1. The molecule data type was completely redesigned. This was done in response to a growing need of the user community to access substructures in order to develop more sophisticated programs dealing with molecules. The redesign makes it feasible for more complicated substructure search and structure-activity types of investigations to be undertaken in PROPHET.

2. In an additional attempt to meet the needs of the PROPHET molecular community, a disk-based molecule capability was introduced. Normally, a molecule is entirely contained in core memory and is consequently limited in size. This had been satisfactory for a number of years, but users increasingly express their need to work with much larger molecules (e.g., proteins). The disk-based molecule capability was introduced to meet this need. In it, most of the information about the molecule is stored on disk-based table files, thus freeing molecules from the limits of core memory size.

3. In conjuction with the new molecule design, a battery of new vector and matrix routines was introduced to speed up the three-dimensional transformations needed to display and manipulate molecular representations. In addition, many of the vector and matrix routines were incorporated in PROPHET's statistical procedures for another increase in efficiency.

4. A major extension was made in PROPHET's curve-fitting capabilities. Procedures were developed to interface PROPHET with MLAB (Modeling Laboratory Program developed at DCRT, NIH) to fit series of differential equations and to extend greatly the complexity of functions which can be fitted from PROPHET.

5. New statistical procedures were added to PROPHET's repertory. These include: Friedman's multiple comparison test; Dunnet's multiple comparison test; and Bartlett's variance test.

6. A major extension was made in the ability to select portions of a table--both in displaying a table, or in making a new table from pieces of another. This new language capability makes the table syntax completely flexible to the user and greatly simplifies what the user needs to do in order to select portions of a table.

7. An interface was developed to the CELLSIM Cell Kinetics Modeling Program. This Program had been requested by several PROPHET users as the best Program available for the simulation of normal and cancerous cell growth.

E. Major Projects

1. Molecular Basis of Antibody Specificity and Its Genetic Control

Dr. E. A. Kabat of Columbia University and NCI and Dr. T. T. Wu of Northwestern University have been using the PROPHET system for approximately five years in support of their collaborative research. Their joint investigations are designed to elucidate the molecular basis of antibody specificity and its genetic control. Thus, the work is relevant to essentially any area of biology and medicine where an organism's immune system may play a role in combating (or, in some cases, causing) disease or dysfunction. Among the questions these investigators are concerned with are the following:

a. What structural features enable antibodies to be so incredibly specific in their associations with antigens?

b. What significance should be attributed to the fact that all immunoglobulin molecules have many structural features in common, irrespective of the antigen against which they are directed or the animal species from which they are obtained?

c. What are the implications of our understanding of antibody structure on the behavior of genetic material?

d. In view of the absence of detailed x-ray crystallographic findings of the three-dimensional structure of immunoglobulin molecules, to what extent can one use knowledge of the primary structure of these proteins (i.e., the linear sequence of amino acids which comprise the polypeptide chains) to make predictions about an antibody's molecular conformation?

In support of their research these investigators have created a unique collection of data relating to the amino acid sequences of the immunoglobulins and their activity. This data base has proven so unique that it is published and distributed worldwide. The collection contains virtually all published sequences of immunoglobulins.

2. NICHD Contraceptive Studies

The Contraceptive Development Branch of the NICHD is currently using PROPHET to aid in the management of its drug synthesis program. Results of biological evaluations of hundreds of new compounds each year are entered into the system, analyzed, and stored in such a manner as to facilitate comparison of new data with old.

A rather simple but elegant routine for keeping track of the numerous analogs of the peptide hormone, LHRH, has also been devised and enables the Branch, when a new analog is proposed by a contractor, to quickly check if the compound has already been synthesized. This system makes use of an alphanumeric representation of the peptide. A similar approach is now being developed for steroids in order to reduce the time required for substructure searches.

BMDP Biostatistical Computer Programs

The BMDP set of statistical computer programs, supported by the BRP under contract with the Department of Biomathematics, U.C.L.A., continues to serve a broader audience with new and improved programs.

The new programs for 1979 include stepwise logistic regression, K-means cluster analysis and balanced mixed model analysis of variance. All programs are now served by a new, more powerful transformation processor. Programs under development include spectral analysis and Box-Jenkins time series analysis, Cox models for survival analysis and multivariate general linear model analysis. Development of these programs has been guided by consultants from other institutions including Dr. John Tukey of Princeton University, Dr. George Tiao of University of Wisconsin at Madison, and Dr. G. W. Stewart of University of Maryland.

During the past year the 1979 edition of the BMDP Manual and many supporting technical reports were issued. A BMDP Digest and Pocket Guide will be issued shortly. Newsletters are issued approximately two times a year. In the last year, versions of BMDP were completed for the following computers: VAX, PDP-11, PDP-10, PDP-20, CDC, XEROX, UNIVAC 70, 90, and 1100, SIEMENS, HP-3000, Burroughs Large Systems and ICL 2000.

Short courses and seminars on BMDP programs were conducted in the United States, Canada and Western Europe. Additional tutorials are scheduled for the United States and Eastern and Western Europe in the late summer and early fall of 1979.

Guidelines for improved documentation and coding of BMDP programs are now being established. A preliminary set of these guidelines are being used at present. Input and encouragement from the BRP/BMDP advisory group has played an important role in the development of these guidelines.

A set of guidelines for enhanced communication between the BMDP group at U.C.L.A. and the statistical community were developed by the BRP/BMDP advisory group. These guidelines guarantee a wider participation in the selection and development of programs and features in future versions of BMDP.

Fiscal Year 1979
Annual Report
General Clinical Research Centers Program
Division of Research Resources

Background and History

The GCRC program was founded in 1959 through action of the Senate Appropriation Committee, which expresseed the belief that national clinical research resources were inadequate. The Committee recommended that Clinical Research Centers be established throughout the country to improve and intensify the scientific attack on man's diseases and their basic biologic parameters. Appropriations increased rapidly from 3 million dollars in fiscal 1960 to 33 million dollars by fiscal 1963. Program expansion was rapid and by 1966 93 centers had been established, with more than 1100 approved beds.

Following this rapid expansion a number of problems became apparent. Many centers could not fully occupy all of the beds which had been dedicated to clinical research. Questions were raised about the propriety of the Federal Government subsidizing the care of sick patients who are also research subjects. The need for research outpatient facilities as a complement to research inpatient facilities became increasingly apparent. At about the same time increased concern with the protection of human subjects began to surface. The complexity and paper work of doing clinical research projects intensified. Peer review procedures began to identify the centers whose clinical research activities were of marginal scientific merit.

In 1969 and 1970 a number of programmatic changes were implemented to correct these deficiencies and improve the overall scientific performance of the program. In 1969 the service patient policy was implemented. This policy had two objectives. The first was to require that the third party carriers reimburse the Centers for those patients who were sick enough to require hospitalization (B patients), while preserving the principle that NIH would continue to pay all costs for those patients hospitalized primarily for research. The second objective of the policy was to reduce the cost of temporarily unoccupied research beds by allowing hospitals to utilize some of them for non-research patients (C patients). The policy was written in such a way as to insure that the use of the centers for C patients did not disrupt the research activity by requiring a disproportionate share of the NIH research resources, nurses and dietitians. At first the service patient policy was accepted reluctantly, but now it is fully accepted and implemented throughout the program.

In 1978 the B patient program recorded 55,000 B patient days, which relieved the program of an estimated 8 million dollars in cost. C patients generated an additional 2 million dollars in revenues to help offset the costs of running the centers. There have been continued concerns that inappropriate application of the service patient policy might force investigators to do clinical research only on sick patients during periods of fiscal constraint. This would be detrimental to fundamental clinical

research efforts aimed at basic understanding of pathophysiology. Thus, the program has remained adamant in its position that scientific merit of the research protocol is the only acceptable criterion for prioritizing patient admission to the centers. Availability of third party payments may not be considered as a criterion for admission.

The use of B patients to help offset the cost of running the program showed a steady increase from 1970 to 1977 (Table 1), but showed no increase between 1977 and 1978, and it is unlikely to increase much in the future. Most likely no increase in the financial relief can be obtained from B patients revenues without altering the criteria for admission to the centers.

A second major change instituted in the program in 1970 was the provision of outpatient research facilities within the existing centers. Unused bed space was converted to examining rooms and existing personnel on the centers were retrained to provide logistical, nursing, and dietary support for outpatient research studies. The outpatient program proved successful, as well as highly productive. Moreover, it effectively utilized space and personnel resources already present. This aspect of the program has shown a steady growth, from 1,200 outpatient visits in 1970 to 76,000 outpatient visits in 1979. The outpatient research element of the program contributed to 1200 publications and 721 abstracts in 1977 alone.

A third major change in the program was the implementation of the mixed center concept, a derivative of the service patient policy. This concept was developed to counter the relatively high per patient cost of maintaining a discrete area with only a few beds. In some instances we have found that the bed base can be enlarged by admitting selected non-research patients with relatively undemanding requirements for care. Mixed centers require much cooperation between the program and the host hospital, but they have made clinical research units possible in institutions where a fully dedicated clinical research center is not cost-effective.

During the 1970s, application of these policies together with intensified scientific peer review has resulted in a program substantially different and improved from its counter part of 10 years ago. In 1969 there were 92 centers with 1016 beds, with a mean priority score of 251. Since 1969, 32 of these centers with 269 beds, at a mean priority of 310, have been terminated. The remaining 60 centers funded in 1969 with 757 beds have been reduced to 523 beds. The space for the 234 beds eliminated from these 60 centers has been converted to outpatient space, revenue producing C patient space, and storage. The outpatient space, including treatment rooms, waiting rooms, examining rooms, and offices, was staffed by existing center personnel. The 20,000 C patient days per year generate about two million dollars in revenue, helping to offset the personnel cost of operating the centers. It has been contemplated that the remaining storage space could be used for CLINFO and data management support staff for the centers. However, this has been possible in only a few instances. During the ten year period since 1969, 12 new centers, with 82 beds, have been

TABLE 1

PATIENT DAYS, OUTPATIENT VISITS AND ESTIMATED SAVINGS FROM B AND C PATIENTS

FY	A Patient Days	B Patient Days	C Patient Days	Total Days	Outpatient Visits	Estimated Savings 4/
70	199,911	25,577	19,336	244,824	1,175	$ 1,596,769
71	194,162	22,293	18,415	234,870	14,515	2,410,559
72	198,810	22,832	16,510	238,152	23,654	2,969,756
73	184,711	22,373	20,417	227,501	36,280	3,065,532
74	180,778	27,485	24,271	232,534	50,614	3,745,804
75	165,513	35,475	22,281	223,269	50,020	4,699,883
76*(12 mo.)	146,418	49,700	26,370	222,488	56,217	7,724,981
77	127,936	54,856	22,075	204,369	65,130	8,437,488
78	116,116 1/	55,362 1/	21,673 1/	193,151 1/	70,588 2/	9,773,615
79	114,668 3/	57,312 3/	26,352 3/	198,311 3/	76,042 3/	10,000,000E

1/ actual as of June 30, 1979
2/ actual as of November 30, 1979
3/ actual through June 30, 1979
4/ includes estimated savings for B patient ancillaries

* 14 months - A - 170,870 B - 58,003 C - 30,775

added to the program, with an average priority score of 207. Five of the 32 centers which were terminated have reapplied and successfully competed for 27 beds.

In summary, then, in 1969 the program supported 92 centers with 1016 beds with an average priority score of 251, while in 1979 it supports 75 centers, with 613 research beds and 76,000 outpatient visits, with an average priority of 213.

Program Content and Quality

The program supports 80 percent of the research inpatient care for the NIH categorical Institutes. More than 3,000 projects are conducted on the centers each year by an even number of investigators, most of whom receive support from research grants, training grants, program project grants, NIH contracts, or career development awards. Thus except for the larger clinical trials the program content is reflective of the NIH clinical research program as a whole. More specifically, in 1975 investigators using the centers were supported by 1907 NIH grants and contracts totalling 204 million dollars (Table II). A similar analysis of 20 centers in 1977 showed a similar pattern of support; by extrapolation, we estimate that in 1977 investigators using 82 centers were recipients of 246 million dollars in NIH grants and 35 million dollars in support from other DHEW agencies, research foundations and societies, industry, and other sources.

Another way of looking at program content is by broad disciplinary categories (trans-NIH activities). In 1977 the centers reported 433 projects costing $10,150,000 in nutrition; 578 projects, costing $7,242,000 in genetics; 330 projects, costing $5,962,000 in diabetes; and 91 projects costing $1,540,000 in arthritis. Of course, these categories (e.g., nutrition and diabetes) are not mutually exclusive, but they do give some idea of program support in a few research areas of great public interest.

Measures of program quality are somewhat more difficult to make, since one is always confronted with the question, "Compared to what?". In terms of publications, the program has had a more than 50 percent increase in output since 1970 (Table III). Moreover, there has been a steady increase in publications resulting from outpatient studies. Thus, the program seems to be far more productive than it was ten years ago despite the substantial decrease in the number and size of centers supported.

A recently completed priority score study provides some information on the level of quality. At the site visits, investigators using the center are ranked on a scale from 100 to 500, like that used by the NIH study sections, by site visit teams which are composed of national experts in the fields being reviewed and which are comparable to the NIH study sections.

In this study, the priority scores awarded to individual investigators at site visits in 1976 were compared with their utilization of bed-days and outpatient resources in 1977. In 14 consecutively reviewed centers, 82% of the patient days were utilized by investigators whose work had been

TABLE II

Estimated Non-GCRC Support for Investigators Using GCRCs by Institute FY 75

Institute	Number of NIH Grants and Contracts Awarded to Investigators Using GCRCs	Awarded Dollars (Millions)
National Institute of Allergy and Infectious Diseases	134	0.8
National Institute of Arthritis, Metabolism and Digestive Diseases	659	40.2
National Cancer Institute	290	45.3
National Institute of General Medical Sciences	112	16.8
National Institute of Child Health and Human Development	187	15.6
National Heart, Lung and Blood Institute	377	70.6
National Institute of Neurological and Communicative Disorders and Stroke	50	7.4
National Institute of Mental Health	38	2.4
National Eye Institute	29	2.2
National Institute of Dental Research	12	0.6
National Institute of Aging	8	0.8
Other	11	1.6
Total	1907	204.3

TABLE III

CENTER PUBLICATIONS

Year	Publications	(Publications Involving Outpatients)	Abstracts	(Abstracts Involving Outpatients)
1969	2,077		931	
1970	2,341		966	
1971	2,219	(246)	991	(122)
1972	2,462	(411)	994	(168)
1973	2,360	(549)	1,176	(285)
1974	2,789	(786)	1,458	(402)
1975	2,993	(935)	1.510	(496)
1976	3,348	(1,120)	1,626	(661)
1977	3,282	(1,228)	1,752	(721)
1978	3435	(1,130)	1,962	(743)

assigned priority scores at the DRR site visit; 18 percent of the bed-day utilization was for new investigators. Of the usage for investigators assigned a priority score by DRR reviewers, about 61% was by those who received a priority score between 100 and 200 at the site visit, and 31 percent was by investigators who had received a priority between 201 and 250. Only 8 percent of the patient day usage was by investigators who received a priority of 260 or higher. The 92% of reviewed investigators whose scores were 250 or better is very similar to the 95% recorded for funded R01 research grants in fiscal 1976. Considering the difficulties involved in doing clinical research, and the importance of clinical trials, which generally receive lower priority scores for scientific novelty, this comparison shows that the work done on GCRCs is similar in scientific quality to that in the research grants program. A previous study established that DRR site visitors award essentially the same average priority score (197) for protocols presented by grant and supported GCRC users as the DRG study section members do for these investigators' research grants in the same scientific areas. The data from these sampling studies indicate that the quality of the work performed on the GCRCs is being effectively maintained by the institutional and national review systems.

Budgetary History

Attached (Table IV) is a ten-year budgetary history of the program, showing the number of beds, number of centers, the appropriation, and the number of personnel supported. The inflationary factors in the program have been somewhat greater than those in the general economy during the past ten years. For expample, the cost of personnel has increased at an annual rate of 9 percent per year for the past ten years, and is expected to continue at this rate at least through next year. The cost per position per year is shown in Table V.

Hospitalization costs have increased at an even more rapid rate, averaging over 13 percent. Between 1972 and 1977 these cost increases were somewhat ameliorated by recoveries from the service patient policy, but current analyses indicate that additional revenue from this source cannot be expected without substantially altering the program content and sacrificing program quality.

TABLE IV

GCRC PROGRAM, 1969 - 1979

FY	CENTERS	POSITIONS FTE	FUNDED BEDS	PATIENT DAYS A + B + C	APPORTIONMENT (in thousands)
69	93	2,298	1023	245,943	$ 35,004
70	93	2,076	904	244,824	35,004
71	82	1,885	881	234,870	38,004
72	84	1,867	907	238,152	42,181
73	83	1,790	893	227,501	41,300
74	87	1,795	877	232,534	42,320
75	84	1,732	823	223,269	42,619
76	84	1,727	784	222,488 1/	42,533
77	82	1,679	755	204,369	47,283
78	79	1,706	633 3/	193,151 2/	51,946
79	74	1,622	613 3/	198,000	51,941
80	75	--	600 4/	--	56,720 4/

1/ 12 month period
2/ actual as of June 30, 1979
3/ excludes 73 beds used for C patients included prior to 1977
4/ estimate

TABLE V

GCRC COST DATA

FY	CENTERS	POSITIONS FTE	COST/POSITION/YEAR	% INCREASE
69	93	2,298	$ 8,334	
70	93	2,076	9,244	10.9
71	82	1,885	10,228	10.6
72	84	1,867	10,228	7.4
73	83	1,790	11,746	6.9
74	87	1,795	12,785	8.8
75	84	1,732	13,750	7.5
76	84	1,727	15,021	9.2
77	82	1,679	16,551	10.2
78	79	1,706	17,852	7.9
79	74	1,622	19,427	8.8
80 1/	75	---	---	---

1/ estimate

Research Accomplishments

Hypertension (I)

A kidney prostaglandin, prostacyclin, has been found to directly affect blood pressure, and may be an important factor in hypertension. It acts by regulating the secretion of renin, a kidney hormone that increases blood pressure. This raises the possibility that specific drugs which inhibit prostacyclin formation might represent new ways of controlling hypertension.

Hypertension (II)

A novel experimental anti-hypertension drug, Captopril, acts by blocking formation of the potent blood pressure-raising hormone angiotensin II, Captopril can lower blood pressure in many patients with either renovascular hypertension, hypertension due to renal failure, or essential hypertension resistant to multiple combinations of other drugs.

It has also been found that the action of Captopril is dramatically potentiated by addition of diuretics, because it blocks activation of the renin system, which is one of the ways in which the body normally resists the action of diuretics. Captopril itself is a mild stimulus to sodium excretion, at the same time that it helps the body conserve potassium. This is because Captopril reduces the secretion of aldosterone, the most potent salt-retaining hormone of the adrenal gland.

In summary, these studies have outlined the mechanisms of action and demonstrated the safety and efficiency of a new drug of great practical value to practicing physicians and the large hypertensive population.

Prenatal diagnosis of thalassemia

A new technique which identifies hemoglobin genes in fetal cells taken from amniotic fluid can be used to detect different forms of thalassemia, a debilitating blood disease which occurs predominately in Mediterranean peoples. The method may also be applicable to prenatal diagnosis of conditions such as immunoglobulin diseases, sickle cell anemia, hemophilia, or other genetic conditions.

Artificial fat

An artificial fat, sucrose polyester, appears to be a safe, effective, non-caloric, well-tolerated cholesterol-lowering agent. It works in high or low cholesterol diets, and does not change the consistency of food containing it.

Ventricular tachycardia

Computerized methods have been developed to make a classification of ventricular tachycardias, or excessively rapid heart action. Specific drugs have been tested and found effective for some of these conditions.

Lyme arthritis

A new tick-borne srthritis has been discovered. It is similar to rheumatoid arthritis but has a characteristic skin lesion and includes neurologic involvement in the early stages. Studies are underway to determine the etiologic agent carried by the tick, possibly a virus. The ticks involved feed on a variety of animals, but the presence of household pets, particularly cats, increases the risk of exposure.

Connective tissue diseases

Patients with any one of a number of rheumatologic conditions are benefitting from new diagnostic tests. The new tests are important primarily in identifying patients who have mixed connective tissue disease, a relatively benign and manageable condition, rather than the more serious disseminated lupus erythematosus, which requires intensive therapy.

Diaphragmatic pacemaker

Patients with the primary hypoventilation syndrome, or "Ondine's Curse" are subject to respiratory arrest during sleep. Now a new instrument, adapted from the cardiac pacemaker, artificially stimulates the phrenic nerve and maintains respiration. This miniaturized device frees quadriplegics and patients with Ondine's Curse from mechanical aids such as iron lungs, rocking beds, tank respirators, and endotracheal breathing devices.

Carcinogen-producing enzymes in the skin

Coal tar products, which are used extensively in treating dermatologic conditions, contain numerous polycyclic aromatic hydrocarbons, including the notorious chemical carcinogen benzo(a)pyrene (BP). New studies show that topical coal tar, and particularly its BP constituents, markedly increase the activity of skin aryl hydrocarbon hydroxylase, an enzyme which plays an important role in the activation of polycyclic hydrocarbons into reactive moieties which can bind to DNA and which may directly induce cancer. These studies suggest that the application of coal tar solution in doses ordinarily used in treating skin disease could induce carcinogenic responses in skin, or, after percutaneous absorption, in other tissues as well.

Insulin delivery systems

A wearable mechanical pump, no larger than a paperback book, can inject insulin under the skin of a diabetic person slowly enough to mimic the output of a normal pancreas. A patient-activated switch delivers a pre-programmed increased dose before meals. With this pump, fluctuations in blood sugar are considerably less than when insulin is administered by the usual method of one or two manual insulin injections per day. It is believed that this more precise control of blood sugar levels will be a means of preventing or delaying the onset of the complications of diabetes. The pump has been successfully tested over periods of up to two weeks in ambulatory patients; more sophisticated versions would be completely implantable and remotely controlled by the patient, with no wires or tubes breaking the skin. These later versions may also involve glucose sensors for automatic feedback control of the blood sugar.

Sickle Cell trait

Growth and development has been shown to be normal in asymptomatic carriers of the sickle cell gene. A new study avoided the methodologic flaws of previous studies which reported impaired physical growth and cognitive development in these individuals, and removes the stigmata attached to this clinically benign trait. Only when two genes for sickle cell hemoglobin are present in the same individual, and frank sickle cell disease develops, is growth affected.

Heart transplantation

The five-year survival rate of cardiac transplant patients operated on since 1973 is projected at 50 percent. This compares favorably to graft survival rates for recipients of renal grafts from unrelated donors. Restoration of physical and psychosocial function has been highly gratifying in 91 percent of 74 patients who lived one year or more after the transplant.

"Accelerated graft arteriosclerosis" is a late complication of cardiac transplantation which sometimes requires a second transplant. Risk factors which have been identified for this condition include donor age greater than 35 and mismatching at the HLA-A locus, especially for A2 and A3. Knowledge of these risk factors can be used to decrease the frequency of the complication.

Pesticide toxicity

It was previously found that elimination of Kepone from the body is speeded by administration of a resin called cholestyramine. Of new interest is a finding that excretion of Kepone either naturally or as stimulated by cholestyramine will ameliorate the signs and symptoms of its toxicity. Possibly of even more importance is a demonstration that the cholestyramine method is also effective in stimulating the removal of chordane, another, more widely used toxic pesticide. The resin may be of general use as a detoxifying agent for materials taken up by the liver.

Program Progress

The Program continues to receive applications for both inpatient and outpatient resources from institutions without General Clinical Research Centers. Three institutions are in the process of preparing inpatient applications. One dental outpatient center has been approved for funding, and additional insitutions have inquired about the establishment of General Clinical Research Centers. Approved new applications will compete with continuation applications for funding, to the limits of available appropriations.

The Program continues its interest in clinical research manpower development. The Clinical Associate Physician (CAP) Program, a post fellowship program intended to develop clinical investigators, now in its sixth year, has attracted condidates of high quality. There are currently 30 CAP positions. Of the 31 CAPs who have completed the program, 27 are continuing academic careers, while four have gone into private practice.

CLINFO

The CLINFO system, a computer based data management system designed for clinical research applications, has been widely accepted by the clinical investigator community and a diffusion program is underway. Bolt, Beranek and Newman has been competitively selected as the purveyor for the system, and CLINFO awards have been made to Duke and Johns Hopkins Universities. The Program currently has 12 additional approved applications awaiting funding.

Core Laboratories

Core Laboratories have undergone intensive review during the last four years with a reduction in the average number of technical positions funded. Program plans call for wider application of newer technology, such as CLINFO, Gas Chromatography-Mass Spectrometry, and high pressure liquid chromatography as core laboratory functions.

Clinical Trials

The Program is currently studying a two-year study by the Rand Corporation entitled "The Evaluation of the Role of Clinical Trials, with Emphasis on Information Processing". The goals of this contract are to 1) determine how clinical trials of different sizes differ in methodology, computer requirements, and need for support personnel; 2) determine how clinical trials are designed and controlled; 3) evaluate the extent of collaboration, the difficulties (e.g., allowing the investigators access to the compiled data base), and how these will impact on the clinical trials performed in CRCs; 4) characterize data management systems used in clinical trials at present, determine what problems were encountered in establishing such systems, and recommend how computer-based data-systems can improve the format of a trial; 5) determine the role of specific aids in administering clinical trials (e.g., keeping records, generating reports, admitting patients).

Administrative Coordinators

Administrative Coordinators have worked closely with Grants Management staff to sponsor orientation sessions for new Administrative Coordinators, and are currently working with Program and Grants Management staff to develop an agenda for their biennial meeting.

Nurses and Dietitians

The nurses and dietitians are an important component of the personnel resource supported by the GCRC Program. These professionals, aware of the critical nature of their contribution to the clinical research process, have organized the National Association of Research Nurses and Dietitians. The Program proposed to investigate the potential value of a workshop at which the unique characteristics of research nursing and dietetics would be discussed, and organized in a meaningful manner to benefit the GCRC Program.

Fiscal Year 1979
Annual Report
Biomedical Research Support Program
Division of Research Resources

The Biomedical Research Support Program administers two institutional research grant programs, the Biomedical Research Support Grant (BRSG) Program and the Biomedical Research Development Grant (BRDG) Program.

BIOMEDICAL RESEARCH SUPPORT GRANT PROGRAM

BRSG awards are made to institutions that receive each year at least three allowable Public Health Service (PHS) research grants totalling at least $200,000. The amount of each award is computed by a formula that is applied to the total dollar amount of allowable PHS research grants during the previous Federal fiscal year. BRSG funds are used for those direct costs of biomedical research that are not feasibly supported by other PHS research grants, or that are supported most efficiently and at least cost with BRSG funds. The objectives of the program are to enhance the quality of biomedical research, increase its productivity, and reduce its cost.

On January 22, 1979 President Carter submitted to the Congress his budget request for FY 1980 which included funds for the Biomedical Research Support Program. This is the second consecutive year that support for the program has been requested by the President.

A revised BRSG General Policy and Information Statement dated April 1, 1979 was issued with the 1979 BRSG awards.

On December 7, 1978, the Director, DRR, requested the Biomedical Research Support Subcommittee of the General Research Support Review Committee to develop long-range plan recommendations for the BRSG and BRDG Programs. The report, dated June 28, 1978, was developed through the efforts of a work group from the subcommittee, the full subcommittee, and the Biomedical Research Support Program Work Group of the National Advisory Research Resources Council (NARRC). The long-range plan recommendations were a source of advice in developing the BRS Program section of the DRR Five-Year Plan, 1982-1986. The Five-Year Plan will be presented to the Director of NIH after it has been discussed by the NARRC at its meeting of October 24-26.

Four regional meetings of program directors with BRS Program staff were held during the year; in Shrewsbury, Massachusetts for institutions in Massachusetts and Rhode Island, San Francisco for institutions in northern California, Los Angeles for institutions in southern California, and Houston for institutions in Texas and Louisiana. This continues a practice that was begun in 1978 and will

continue in 1980. The regional meetings have resulted in better understanding of program objectives and policies by grantees and better management of awards by grantees and the DRR.

The following tables describe the utilization of BRSG funds, the amounts available, and their allocation to grantees.

TABLE I

BRSG Expenditures by Activity FY 1977

	Number	Dollars (in thousands)	% of Total Dollars
RESEARCH PROJECTS	9,565		
Pilot Projects	5,098	13,503	30.8
Regular Projects	4,467	16,882	38.5
CENTRAL RESOURCES		10,897	24.8
OTHER ACTIVITIES		2,608	5.9
TOTAL		43,890	100.0

TABLE II

FUNDING HISTORY
Biomedical Research Support (BRS) Program
(Dollars in thousands)

Year	A Funds Available for NIH Research Grants 1/	B BRS Authorization Ceiling (15% of Funds Available for NIH Research Grants)	C BRS Appropriation	D Column C as a Percent of Column A
1966	$ 604,377	$ 90,657	$ 45,200	7.5
1967	681,197	102,180	51,700	7.6
1968	727,366	109,105	59,700	8.2
1969	729,230	109,385	60,700	8.3
1970	744,061	111,609	57,677	7.8
1971	765,510	114,827	54,200	7.1
1972	901,119	135,168	55,212	6.1
1973	925,457 1/	138,818	60,700 2/	6.5
1974	997,878	149,681	45,149 3/	4.5
1975	1,142,783	171,417	42,957	3.7
1976	1,272,771	184,465	42,957	3.5
1977	1,419,821	212,973	40,873 4/	2.9
1978	1,610,036	241,505	40,873 4/	2.5
1979	1,868,551	280,282	45,021 4/	2.4

1/ Thru 1972 includes NIMH

2/ Includes 33.5 million impounded funds

3/ Excludes Minority Biomedical Support Program funds after 1973

4/ Includes Biomedical Research Development Grant Funds

TABLE III

Distribution of BRSG Awards by Size

Size of BRSG Award (in thousands)	Number of Grantee Institutions			
	FY 1976	FY 1977	FY 1978	FY 1979
Under - $ 30.0	74	94	93	78
$ 30 - 49.9	87	89	89	93
50 - 99.9	116	115	106	105
100 - 149.9	60	69	79	82
150 - 199.9	48	37	30	41
200 - 249.9	19	51	48	58
250 - 299.9	37	--	--	--
TOTAL	441	455	445	457

Grant Range	Amount			
	FY 1976	FY 1977	FY 1978	FY 1979
Low	$ 17,418	15,565	14,198	14,441
High	261,305	213,709	200,462	201,413
Average	96,955	86,754	86,117	91,359

TABLE IV

Total Entitlement* Compared to BRSG Funds Awarded

Fiscal Year	Entitlement*	BRSG Funds Awarded	Ratio BRSG/Entitlement
1976	$ 995,465,535	$42,957,000	4.32%
1977	1,060,171,080	39,473,000 1/	3.72
1978	1,153,259,633	38,322,272 1/	3.32
1979	1,324,013,741	41,751,118 1/	3.15

*Total allowable PHS grants used for computation of BRSG awards

1/ Excludes Biomedical Research Development funds

TABLE V

Distribution of BRSG Awards by Type of Institution

Type of Grantee Institution	FY 1973	FY 1974	FY 1975	FY 1976	FY 1977	FY 1978	FY 1979
Medicine	104	104	107	106	107	109	109
Dentistry	34	33	34	26	27	31	29
Osteopathy	0	0	1	1	1	1	1
Pub. Health	12	12	12	12	13	13	12
Pharmacy	14	12	17	13	14	12	13
Veterinary Med.	15	14	15	10	11	10	10
Nursing	3	4	5	3	2	4	5
Allied Health	1	1	1	0	0	0	0
Optometry	0	0	0	0	0	0	1
Hospitals	71	66	71	63	61	59	61
Health Dept.	2	2	2	2	1	1	2
Research Inst.	71	70	75	71	71	67	67
Other Academic 1/	113	108	121	134	147	138	147
TOTAL	440	426	461	441	455	445	457

1/ Academic institutions other than health professional schools

BRSG awards are used for a wide variety of purposes, some of which are illustrated by the following examples.

BRSG funds provided supplemental support to Dr. Neil G. Ingels of the Palo Alto Medical Research Foundation, for supplies, instrumentation, and partial salary support in the development of a technique to measure cardiac function by x-ray motion picture studies of movements of tantalum coil markers placed in heart muscle at the time of surgery. This technique, which does not have the drawbacks and risks of other techniques, provides important information on the success of various types of heart surgery, and the response of the heart to exercise, drugs, Valsalva manuever, etc.

An investigator at the University of California at Los Angeles School of Dentistry, developed with BRSG support a tissue culture model of osteogenesis. The model replicates development of woven and lamellar bone. It has been used in studies of bone physiology and pathology, including virus induced osteosarcoma, a malignant tumor of bone. Studies using this model are being supported by research project grants, and findings from such studies, following peer-review of their validity, have been published in scientific journals.

BIOMEDICAL RESEARCH DEVELOPMENT GRANT PROGRAM

The BRDG Program is a competitive institutional grant program intended for institutions that have limited health research capability, have significant health manpower training responsibility, are committed to improving and sustaining their health-related research, and offer strong potential for high quality health-related research. The objective is to strengthen and/or expand health-related research in eligible institutions provided it will result in improving the training of manpower for clinical health professions or health-related research or both.

Nine new BRDG awards were made in 1979, bringing the total number of awards to 32. The new and continuation 1979 awards total $3,133,229. The numbers awarded to each type of institution are:

TABLE VI
BRDG AWARDS AS OF 9/30/79

School of Medicine	8
School of Dentistry	3
School of Osteopathy	3
School of Pharmacy	6
School of Veterinary Medicine	3
School of Nursing	1
Other Academic	3
Hospital	2
Research Organization	3
	32

During the course of the three completed review cycles, 174 applications have been reviewed. As a result of reapplication by previously unsuccessful applicants, there have been 137 different institutions that have applied.

Some accomplishments of the BRDG Program are illustrated by the following examples.

BRDG funds were used at one institution for recruitment of investigators, release time for research by existing staff, and purchase of research equipment. During the first year of BRDG support, 18 projects were initiated and during the second year, an additional seven projects. Two of the projects are now supported by research project grants, and three other project grant applications are pending review.

At a new medical school, the BRDG award assisted in the attraction of research oriented faculty. The BRDG support enabled the institution to increase the number recruited to 32, and to provide them with initial research support immediately upon entering on duty.

TABLE VII

NUMBER OF INSTITUTIONS
WHICH APPLIED FOR
BRDG PROGRAM 1/

	Fiscal Year '77	'78	'79	Total Institutions	Total Funded
Allied Health	0	1	2	3	0
Dentistry	14	7	3	24	3
Hospitals	5	5	1	11	2
Medicine	14	2	2	18	8
Nursing	1	9	2	12	1
Optometry	0	0	2	2	0
Osteopathy	4	2	1	7	3
Other Academic	8	5	0	13	3
Pharmacy	10	2	4	16	6
Podiatry	0	0	1	1	0
Public Health	2	0	2	4	0
Research Institutes	10	4	3	17	3
Veterinary Medicine	4	4	1	9	3
Total New Applicants	72	41	24	137	32

1/ No Resubmissions Included

TABLE VIII

BRDG PROGRAM
APPROVAL AND FUNDING RATES

FY	Number of Applications	Approval Rate (Percent)	Funding Rate (Percent)
'77	72	31.9	16.6
'78	58	32.7	18.9
New App.	41	19.5	14.6
Resubmission	17	64.7	29.4
'79	44	34.1	20.5
New App.	24	20.8	12.5
Resubmission	20	50.0	30.0

The BRDG General Policy and Information Statement and the Instructions for Preparation of Application have been revised. Both of these documents are dated July 1, 1979.

The NIH Guide for Grants and Contracts, Vol. 8, No. 9, July 6, 1979 announced the October 1, 1979 deadline for receipt of BRDG applications and the intent to accept no applications in 1980 or thereafter. The decision to phase-out the program after the next review was based upon the declining number of applications and the even greater decline in the number of institutions that submit applications for the first time. Funds that will no longer be needed for BRDG awards will be restored to the BRSG Program and/or for new types of research grant support that might be initiated under the general research support authority of the Public Health Service Act, Section 301 (a)(3).

FISCAL YEAR 1979
ANNUAL REPORT
MINORITY BIOMEDICAL SUPPORT PROGRAM
DIVISION OF RESEARCH RESOURCES

GENERAL RESPONSIBILITY

The Minority Biomedical Support (MBS) Program is charged with the responsibility of trying to rectify the problem of the underrepresentation of ethnic minorities in biomedical sciences. Resolution of this problem is approached through the granting of institutional awards focused on providing minorities equality of opportunity to engage in biomedical research. The MBS Program supports projects designed to strengthen biomedical research capabilities of institutions with a significant commitment to minorities, and to increase and expand the involvement of faculty and students in biomedical research.

SPECIFIC OBJECTIVES

The overall mission of the MBS Program is necessary as a result of the dearth of minority scientists. Therefore, the specific objectives of the Program are:

a. to increase the numbers and quality of minority biomedical scientists,
b. to strengthen and develop the research setting (eligible institution) in which biomedical research can be conducted, and
c. to broaden the opportunities for involvement in biomedical research by ethnic minority faculty, students and investigators.

The MBS Program provides funds for released time so that faculty may have the opportunity to conduct biomedically oriented research. Equipment, supplies and necessary renovations for approved research projects are supported by this Program. In addition, funds are provided for student participation in research as well as for consortia, collaborative arrangements, special summer projects, and travel to scientific meetings.

In June 1974, the Director of the National Institutes of Health requested that all Bureaus, Institutes and Divisions initiate and coordinate their minority programs activities through the existing minority programs (i.e., the Minority Biomedical Support Program (MBS),DRR and the Minority Access to Research Careers Program (MARC),NIGMS). It was through this request that the Intra-Agency agreements between the Institutes and the MBS Program were forged.

The initial review of all applications is conducted by the General Research Support Committee and the secondary review is provided by the National Advisory Research Resources Council in cooperation with the National Advisory Council of the Bureau or Institute entering into the agreement. Following the review, the cooperating Institute or Bureau provides support of those components of grants that are congruent with their research thrust.

The purpose of the Intra-Agency Agreements are to place Minority Biomedical Support (MBS) Program investigators in a position to enter the research arena of the cooperating Institute. Via the cooperating agreement, investigators are made more aware of the Institute's research thrust and application requirements and this can place them in a competitive position for research support.

At present the following Institutes have developed Intra-Agency agreements with the MBS Program:

1. The National Cancer Institute
2. The National Heart, Lung and Blood Institute
3. The National Institute on Allergy and Infectious Diseases
4. The National Institute on Aging
5. The National Institute of Dental Research
6. The National Institute of Child Health and Human Development
7. The National Institute of Neurological and Communicative Disorders and Stroke
8. The National Eye Institute
9. The National Institute of Arthritis, Metabolism and Digestive Diseases
10. The National Institute of Mental Health

The Agreements with the National Eye Institute, the National Institute of Arthritis, Metabolism and Digestive Diseases and the National Institute of Mental Health were negotiated during FY 1979.

The Intra-Agency agreements have resulted in the accomplishments presented in Tables 1 and 2. As evident from the Tables, reimbursements have increased from $341,964 in fiscal year 1975 to $4,564,000 in fiscal year 1979. The number of projects supported have increased from 8 in FY1975 to 114 in FY1979.

PROGRAM HIGHLIGHTS

One of the major Program highlights this year was the Annual MBS Symposium held in Atlanta, Georgia, on April 15-18, 1979. About 1500 individuals attended the meeting with the largest percentage being students and investigators. Over 400 scientific research papers were presented. Most of them were presented by MBS student research participants. This year 2 new facets were added; scientific techniques workshops and poster sessions. The poster session was well attended and there were over 100 poster presentations. Several students and investigators participated in the workshops that offerred techniques in: Recombinant DNA, Immunology and Disease, Techniques in Isoelectric Focusing-Polyacrylamide Gel, Radioimmunoassay, Liquid Chromatography, Liquid Scintillation Counting, Cell Culture and Computer Graphics.

Several invited papers were presented by well known minority and non-minority scientists including two Nobel Laureates, Dr. Howard Temin and Dr. Charles Huggins. A number of institutions sent represenatives to the symposium to provide information and recruit minority students into

their graduate and professional programs. In addition, several representatives from NIH were present to provide investigators with information regarding their programs and explain application procedures. The abstracts of papers presented were published in a 179 page journal. Copies of the program and published abstracts are available in the DRR files.

This year at the Annual Program Directors Meeting in Houston, Texas, cost sharing and indirect costs were discussed. This is the first year that the MBS Program is authorized to pay indirect costs. A major emphasis was on the establishment of a work session in which the new MBS Policy and Information statement was developed. In addition, cooperating Institutes sent representatives to the meeting. The major objective of this activity was to have Program Directors present pre-proposals to the proper Institute representative for a critique. This interaction motivates investigators to seek funding through non-MBS channels and the critique provided the investigators with feedback that would improve their grantsmanship relative to the Institute's thrust. The Program Directors Meeting was considered very successful by all concerned.

STAFF VISITS

This year a major emphasis was placed on conducting administrative staff visits to Grantee institutions. MBS Staff conducted 40 staff visits in the past year. The major objectives of the staff visits were to monitor the projects, and assist the Program Director in managing the grant and develop the strongest program possible. Also, the staff visit provided information that was very useful in the making of decisions to determine the level of funding for continuations and renewals. This allowed the staff to phase out some weak projects and start up some new projects.

NEW INITIATIVES

Two-year colleges became eligible to submit applications under new guidelines developed by staff and the advisory groups. Several applications have already been received and two were funded this year.

PROPHET - A new activity was also made possible through an agreement with the Biotechnology program for making the PROPHET computer system available to MBS investigators. At least one PROPHET user site per year will be established at MBS institutions. Workshops and demonstrations will be conducted this fall.

Five Year Plan - Work was begun on development of a five year plan. This involved several meetings of a subcommittee of the General Research Support Review Committee to develop a position paper to assist the DRR in writing the five year plan.

Data Base Management - In order to plan for an evaluation of the program, an effort was initiated to develop a computerized system of data capture for scientific and fiscal data. Accessibility to program and grants management staff is made possible by the use of a CRT terminal in the branch.

ACCOMPLISHMENTS

Several of our MBS students have provided evidence that the Program is reaching fruition. To date, 30 Ph.D. students have graduated and are now doing postdoctoral work at major laboratories. It is not known how many of the 1800 or so MBS graduates since 1973 are still pursuing graduate or professional degrees. Part of the planned evaluation effort will center on tracking MBS graduates.

Faculty investigators are entering the competitive arena at NIH by the regular research grant application route and also by appointments to NIH review and advisory groups. Several MBS investigators were appointed to review committes and one was appointed to the Recombinant DNA advisory committee. There is anecdotal evidence that investigators are gaining recognition.

According to the most recent data available, the MBS Program has achieved the following:

1. There were 315 publications, 320 faculty presentations and 467 student presentations reported in progress reports for FY1978. The results for FY1979 are not complete yet.
2. Career choices of MBS graduates in FY 1978: 147 entered medical school, 24 entered dental school, 113 entered graduate school, and 74 entered other health-related schools.
3. Intra-agency agreements increased substantially; the numbers of projects funded by Institutes increased to 114 for 1979 with 10 Institutes participating.
4. In 1978 the number of positions funded in the MBS Program were 389 faculty, 786 undergraduate students, and 245 graduate students. The Participants are involved in over 400 separate research projects funded by the Program at 80 institutions. In FY 1979 the comparable figures are: 402 faculty; 739 undergraduates, 247 graduate students.

All of the above data indicates that there is a definite trend toward accomplishing the goals of the MBS Program, and one can project that this positive trend will continue.

Detailed information regarding this data is shown on the following tables.

TABLE II

MBS ACCOMPLISHMENTS

PUBLICATIONS AND PRESENTATIONS

1974-1979

	1974	1975	1976	1977	1978*	1979**
Publications	75	163	320	344	315	402
Presentations (faculty)	143	211	339	311	320	358
Presentations	212	398	520	488	467	439

*Data is incomplete for 1978
**Data is incomplete for 1979 (55 grantees reporting)

TABLE II

MBS ACCOMPLISHMENTS

CAREER CHOICES OF GRADUATES

1974-1979

	1974	1975	1976	1977	1978	1979*	Total 1974-1979
Medical School	78	116	150	166	142	147	799
Dental School	13	22	40	24	27	24	150
Graduate School	99	120	174	150	119	113	775
Other Health Related Schools	35	39	87	79	103	74	417
Total Enrolled in Advanced Training	225	297	451	419	391	358	2141
Total MBS Graduates	295	399	648	543	572	421	2878

* Data incomplete (only 55 reports available)

REIMBURSEMENTS - MBS (ACTUAL)

	FY 1975	FY 1976	FY 1976-TQ	FY 1977	FY 1978	FY 1979
Reimbursements:						
NCI	$ 228,268	$ 654,842	$ 131,380	$ 1,137,819	$ 1,465,866	$1,472,704
NHLBI	113,696	526,358	217,847	440,872	1,397,921 1/	1,587,081 2/
NIAID				112,252	114,047	125,858
NIAMD						319,944
NIDR				26,380	32,258	111,327
NIA				177,816	214,962	222,516
NEI						8,458
NICHD					261,853	418,126
NIMH						279,163
NINCDS						50,455
SUBTOTAL	$341,964	$1,181,200	$349,227	$1,895,139	$3,486,907	$4,595,632
MBS Appropriated Funds	7,270,000	7,610,000	1,238,000	9,711,000	10,758,000	14,574,000
TOTAL FOR MBS	$7,611,964	$8,791,200	$1,587,227	$11,606,139	$14,244,907	$19,169,632

*DLD	$ 302,821	$ 337,979
DBDR	52,223	84,225
DHVD	1,042,877	1,164,877
Total	1,397,921 1/	$1,587,081 2/

7/31/78

Table 1 (Con't)

YEAR	INSTITUTE	NUMBER OF PROJECTS	AMOUNT
FY-1978	National Institute of Child Health & Human Development (NICHD)	8	$ 271,991
FY-1979 (Estimated)	National Cancer Institute (NCI)	33	1,471,407
	National Heart, Lung and Blood (NHLBI)	38	1,659,745
	National Institute of Allergy and Infectious Disease (NIAID)	3	125,858
	National Institute of Arthritis Metabolism and Digestive Diseases (NIAMDD)	12	347,694
	National Institute of Dental Research (NIDR)	4	111,327
	National Institute on Aging (NIA)	5	221,705
	National Eye Institute (NEI)	1	8,458
	National Institute of Child Health & Human Development (NICHD)	10	291,950
	National Institute of Mental Health (NIMH)	5	276,106
	National Institute of Neurological Communicative Diseases and Stroke (NINCDS)	3	50,455
SUBTOTAL		114	4,564,705

SUMMARY OF MBS-NIH INSTITUTES
COOPERATIVE FUNDING AGREEMENT FY75-79

YEAR	INSTITUTE	NUMBER OF PROJECTS	AMOUNT
FY-1975	National Cancer Institute (NCI)	5	$ 228,268
	National Heart, Lung and Blood (NHLBI)	3	113,696
FY-1976	National Cancer Institute (NCI)	20	654,842
	National Heart, Lung and Blood (NHLBI)	25	526,358
FY-1976 TQ	National Cancer Institute (NCI)	4	131,380
	National Heart, Lung and Blood (NHLBI)	13	217,847
FY-1977	National Cancer Institute (NCI)	21	1,137,819
	National Heart, Lung and Blood (NHLBI)	11	440,872
	National Institute of Allergy and Infectious Disease (NIAID)	3	112,252
	National Institute of Dental Research (NIDR)	2	26,380
	National Institute on Aging (NIA)	4	177,816
FY-1978	National Cancer Institute (NCI)	33	1,467,410
	National Heart, Lung and Blood (NHLBI)	35	1,456,711
	National Institute of Dental Research (NIDR)	2	35,258
	National Institute on Aging	5	220,262

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

DIVISION OF RESEARCH SERVICES

Fiscal Year 1979

A Letter From the Director

Joe R. Held, D.V.M., Director
Division of Research Services
National Institutes of Health

This year we are endeavoring to make the Division's annual report more useful to those whom we serve. We have shortened the text to focus on information which we feel is of interest and importance to scientific investigators and administrators so that they may better understand the Division's capabilities, its people, and resources in furthering the pursuit of biomedical knowledge.

Specific developments during 1979 are discussed in the context of the array of services and products delivered by the Division's six branches. By familiarizing readers with the work we do, we can become even more effective in providing our wide range of services. In this vein, we are presenting a short essay by Dr. Murray Eden which further clarifies the roles our Biomedical Engineering and Instrumentation Branch staff play in supporting researchers with engineering and physical science skills. (See page 7.)

The Division's various operations are shaped to support the activities of the 12,580 staff members in the 18 Bureaus, Institutes, and Divisions (BIDs) which make up the National Institutes of Health. Our greatest program emphasis, however, is directed at serving the 5,000 staff members of the intramural program, including approximately 2,442 doctoral level scientists, who conduct research in NIH laboratories.

Three of the Division's principal activities also provide technical contributions to the NIH extramural research mission at universities and other facilities. These areas are advanced bioengineering and instrumentation, research animal modeling and breeding, and environmental health and safety in the conduct of research. Many of the innovations, products, and techniques developed by the Division are widely applied in the scientific community, nationally and internationally.

The Division's Organization

In reviewing the year's developments, it should be kept in mind that the Division is organized to provide the highest quality, yet economical, services and products at each of the five sequential steps in every biomedical research project: planning, providing the proper environment, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results.

- The Library Branch possesses or has access to virtually all published biomedical knowledge to assist the investigator in planning and designing his/her project.
- The Environmental Safety and Radiation Safety Branches assure that both the research work itself and the disposal of contaminants are performed in accordance with the highest standards of safety. The Environmental Safety Branch also provides the microbiologic media which serves as a substrate for much research.

- The Veterinary Resources Branch provides the animal models and proper facilities for their use.
- The Biomedical Engineering and Instrumentation Branch collaborates with the investigator in devising the means whereby research materials may be manipulated and results measured, often with highly sophisticated electronic equipment.
- Finally, the skills of the Medical Arts and Photography Branch are available to all investigators to enable them to communicate the results of their research to the scientific community.

A Productive Year

During 1979, nearly all of our output indicators showed an increase in products and services delivered by the Branches—reflecting an intensification of effort by the various NIH Institutes. The dimensions of these support activities can be perceived in the following statistics:

Approximately 1.25 million items were shelved in the Library; 2 million items were photocopied; 7 million pieces of glassware were issued along with 160,000 liters of media; 200,000 millicuries of radioactive materials were received and processed; approximately 14,000 biomedical engineering and instrumentation projects were completed, and nearly 1 million animals were issued. Nearly 400,000 photographs were taken of research work in progress and 40,000 graphic presentations were prepared to record the results of research.

The higher output of products and services was accomplished through greater efficiency, automation, contracting, and overtime. Our permanent staff of 555 employees remained essentially unchanged.

Financial Operations

The Division's budget of $28 million for the year (see Table) reflects the higher costs of producing products and services. During the year, some changes occurred in the financing of services that are of significance to investigators. About $16 million was financed through the Service and Supply Fund, a 33 percent increase over FY 1978. This fund defrays actual charges made to the Institutes for a quantifiable product or service. The remainder of the budget, $12 million, was financed through the Management Fund. This is an NIH fund supported by prorated shares of the Institute's appropriations to provide for central administrative and other services. The Management Fund supports such Division activities as library services, safety services, and other functional areas including the Office of the Director. Animal sales, equipment rentals, instrument shop services, photographic services, central glassware processing, and certain medical arts services are among those funded through the Service and Supply Fund.

During the year, the graphics service of the Medical Arts and Photography Branch was converted from the Management Fund to the Service and Supply Fund. This distributes the costs to those actually using the service, a more equitable arrangement. The conversion of more services to this form of payment is contemplated.

Meeting the Anticipated Demand

The Division sets its own productivity goals. Demand for various services is anticipated by analyzing trends in output. With an organization as large as NIH it is possible to forecast the demand for many services based on past performance. The Division also considers it part of its responsibility to be aware of new technology in the fields we represent and, where applicable, to make new resources available to investigators.

For example, we added several new on line search systems to our library services and increased the production of nude mouse strains to meet expected higher demand. Some services were added during the year by special request, among them a central electron probe facility which is now being used by four of the Institutes.

In establishing our goals and priorities, we rely heavily upon the advice of committees composed of users of our services. These advisory groups presently include the Library Advisory Committee, the Animal Care Advisory Committee, the Radiation Safety Committee, the Genetics Resource Advisory Committee, and the Biosafety Committee. Indeed, we have found this type of advice so useful that plans are underway to establish similar committees in FY 1980 related to our biomedical engineering and instrumentation, and medical arts and photography activities.

New Regulatory Obligations

During the year, the Environmental Health and Safety program's responsibilities were expanded as a result of new legislation, regulations, and policies with which NIH must comply. One example is the process-

ing of Intramural Memoranda of Understanding and Agreement (IMUA's) with investigators for work involving recombinant DNA. The Nuclear Regulatory Commission has added new regulations and policies which require closer monitoring and more detailed record-keeping in the use of radioisotopes. Similarly, attention is being paid to new regulations of the Department of Labor's Occupational Safety and Health Administration. The new Federal Resources Conservation and Recovery Act is demanding much of the Division's time to develop a system to allow NIH to comply with the law in the disposal of chemicals and other materials.

The FY 1980 Outlook

During the coming fiscal year, we anticipate some difficulties associated with the delivery of our services. The shortage of primates, which is international in scope, undoubtedly will cause delays in providing animals for certain studies. Fortunately, our domestic breeding programs are now well underway, and should alleviate the shortage soon.

Planned renovations on the B-1 level of the Clinical Center will extend into the Library and can be expected to cause some inconveniences. Other planned renovations could affect media, glassware, and biomedical engineering and instrumentation services.

A thorough study has been completed of NIH's environmental health and safety activities. A reorganization plan has been developed for implementation in the new fiscal year which can be expected to greatly improve the discharge of NIH's responsibilities in this increasingly complex and highly visible area. It should result in a program which will not only support our scientists in safely carrying out their work, but provide the public with the assurance, to which it is entitled, that unreasonable risks are not being taken in our biomedical research programs.

The Division of Research Services looks forward to another productive year in continuing its support of the NIH staff in all phases of research—and maintaining its high standards of quality.

Division of Research Services FY-79 Budget (in thousands of dollars)

Branch	Management Fund	Service & Supply Fund	Total
Veterinary Resources	$3,336	$6,861	$10,197
Biomedical Engineering & Instrumentation	1,864	5,175	7,039
Library	2,137	—	2,137
Medical Arts & Photography	705	2,831	3,536
Environmental Health & Safety	4,290	872	5,162
Total	$12,332	$15,739	$28,071

Biomedical Engineering and Instrumentation Branch
Murray Eden, Ph.D.

Biomedical Engineering and Instrumentation Branch

During Fiscal Year 1979, the Biomedical Engineering and Instrumentation Branch continued to provide a wide variety of specialized engineering and physical science skills to the NIH research community. More than 200 projects were undertaken collaboratively with intramural NIH programs to produce advanced instrumentation models, methods, and techniques dedicated to the acquisition of biomedical information previously not available to the research scientist.

The Branch's skills span a great range of disciplines. The staff includes some 30 professional physical scientists and engineers as well as 75 technical support personnel: machinists, glassblowers, instrument makers, electronic and mechanical technicians. During the year, the Branch responded to over 3,800 requests from NIH scientists for the fabrication and modification of laboratory devices and made another 8,000 repairs or minor changes to scientific equipment.

Engineering sections engaged in the following activities in support of biomedical research projects:

Chemical Engineering Section—Much of the section's work currently is focused on theoretical and experimental studies that include the analysis of physiological systems and transport phenomena, analytical methodology, biomaterials, and specialized instrumentation.

The section has developed significant new methodology for applying chemical reaction engineering to a variety of pharmacokinetic problems. Its expertise in pharmacokinetic modeling has become a resource integral to the programs and planning of several NIH components. Particular emphasis has been placed on extrapolations from laboratory animals to man in the pharmacokinetics of environmental contaminants and on laboratory and clinical studies of anticancer drugs. A treatment regimen has been initiated for ovarian cancer by intraperitoneal administration of anticancer drugs according to pharmacokinetic principles (see next page). Improvements have been made in a colorimetric pH probe designed for use in tissue and blood. The probe may have applicability in surgery or in an intensive care unit to monitor patient status, such as for the onset of shock.

Electrical and Electronic Engineering Section—The staff of this section is concerned with making available to the NIH intramural research program the full power of modern electronic technology. Activities include design and construction of new devices, assistance with selection and application of commercially available apparatus, systems analysis, contract management, and consultation and communication with NIH researchers and members of the electrical engineering profession. The scope of work embraces analog and digital circuit design, hardware and software design for microprocessor-based "smart" instruments, transduction, feedback control systems, video and radio frequency circuitry and systems, electromechanical and electro-optical systems, and many other fields.

Mechanical Engineering Section—The assistance this section provides to NIH research programs most often consists of specialized and unique instrumentation. Support programs include application of engineering and physical science disciplines in such areas as optics, heat transfer, fluid flow, mechanics, ultrasonic, and machine design to specific bioresearch problems. The consultative and design services supplied to institute researchers are of equal importance. In keeping with our intent to examine and develop new techniques and methodologies which may be significant, the section is exploring fluidic logic, single optic fibers for in vivo implantation, solar lighting, and improved blood pressure measuring techniques based on oscillometry.

Applied Clinical Engineering Section—This section is a multi-disciplinary group physically located within the Clinical Center. Close proximity to the clinical research programs facilitates the interaction between the life scientists and our engineering staff, and permits a more synergistic approach to the problems at hand along with better utilization of the available technology. As an example, in collaboration with the Hematology Branch of the Heart, Lung, and Blood Institute, this section has developed a family of new research tools and methodologies. In addition to these more clinically oriented developments, the section is providing analytical and experimental expertise in the study of such basic areas as solubility and diffusivity of oxygen in sickle cell hemoglobin gels and the rheological behavior of the red blood cell membrane.

Technical Services

Fabrication of special instruments and the modification of equipment are performed in the Branch's shops. The shops are staffed by skilled craftsmen—instrument makers, glassblowers, machinists, welders, electronic technicians, equipment repairers and other specialists.

Since 1979, the Branch has maintained a scientific equipment rental program that has become increasingly popular with NIH investigators. There is a wide variety of instruments among the total of 1,200 presently available. What has made the program a success is the immediate availability of the equipment (items are usually delivered to the laboratory the day after they are selected) requiring little or no capital investment.

Efficiency of the program has been increased by a newly developed computerized recordkeeping system, permitting a 33 percent reduction in rental rates. The program is being further improved by development of an instrument catalogue, which will contain a detailed description of each item, including its operating characteristics and specifications.

Chemical Models, *In Vivo* Measurements & "Smart" Instruments—New Tools for the Biomedical Investigator

By Murray Eden, Ph.D.

Almost invariably, when biomedical research is to be applied to human health problems, it is necessary to predict the effects on man, starting from experimental results on animals. An example is the testing of environmental contaminants for carcinogenicity. Surveillance of selected human populations, such as certain occupational groups, will rarely do because such studies are retrospective and because many years may elapse between the start of exposure and development of cancer. If a chemical in commerce is shown to cause cancer in a mouse or a rat, the now familiar debate concerning the quantitative relevance to man is sure to start.

Similarly, drugs investigated for possible use in the treatment of cancer are first studied in tumor-bearing mice. If a drug is shown to have activity, it undergoes additional pharmacological and toxicological studies in animals before its first use in patients. A variety of questions arise concerning how best to introduce a potentially active agent into clinical practice in terms of timeliness, effectiveness, and safety. One course open to investigators is the development of chemical models.

Model systems are used extensively in engineering. The reason for this is quite simple. They are generally easier (and cheaper) to construct and to manipulate than the prototypes. Phenomena and processes that are modeled may be very complex, and the underlying physics poorly understood. Then, too, notions of dimensional analysis and similitude can be invoked to reduce the number of variables and make the problem experimentally tractable. Models, themselves, may bear a clear geometric similarity to the phenomenon they are intended to model; e.g., airfoils for testing in a wind tunnel or ship hull designs for testing in a towing tank. Alternatively, a model may be a set of mathematical equations which represents the essential elements of a physical or chemical process.

A model may represent only a part of a complex process. For example, in the design of a reactor to produce a chemical change in a fluid mixture flowing through a packed column of supported catalyst, one needs to have quantitative information on heat transfer, pressure drop, mixing, diffusion and chemical reaction. It is frequently possible to uncouple these several processes experimentally and study them independently. Then several model systems are involved, and none of them bears a very close resemblance to the final design.

The biological literature expresses the need for animal models for testing drugs and other chemicals. Such a model is illusory if the goal is *sameness* in the essential elements of chemical absorption, distribution, metabolism. and elimination. There are significant differences among species, but this fact does not invalidate the usefulness of a model system. In engineering, it is axiomatic that the model is *never* the same as the prototype. Similitude does not imply sameness. Rather, model systems can explain those parts of a complex process which cannot be predicted from fundamental principles or obtained from existing correlations. Model-dependent information, then, may be used in conjunction with a considerable body of knowledge and judgment in predicting biological effects.

Extrapolating Effects on Man

There are many similarities in the anatomy and physiology of mammalian species. A general belief in this similarity has been the cornerstone of biomedical research. The same blood flow diagram could be used for all mammals. We mammals also share a remarkable geometric similarity; in fact most organs and tissues are similar fractions of our body weight with the exception of structural components such as skin and skeleton. Major qualitative differences, such as the

absence of a gallbladder in some species, are the exception. Thus, while we must recognize the differences, we may also exploit our understanding of the similarities. For this purpose, chemical reaction engineering forms a natural and clearly articulated basis.

The use of chemical engineering principles may be illustrated by reference to some specific projects. Polychlorinated biphenyls (PCB's) are a ubiquitous and persistent class of environmental contaminants, and the effects of long-term exposure upon man are unknown. In collaboration with biomedical scientists at the National Institute of Environmental Health Sciences, we have developed a mathematical model for predicting (or simulating) the behavior of PCB's in mammals. This model was initially derived from careful studies in the rat and is now being extended to the monkey and dog to validate areas of similarity between these species and to suggest ways to quantitate differences. Then, it will be used to predict expected behavior of PCB's in man.

Kepone is another persistent environmental contaminant. Chemical workers, poisoned by high exposure to kepone, have been treated by oral administration of a material which absorbs kepone and accelerates its elimination from the body. Our calculations, based on a study of the distribution and disposition of kepone in the rat, suggest that the rate of removal from patients could be greatly increased if we had a more effective sorbent.

As a final illustration, the development of a new treatment for ovarian cancer may be cited. We have collaborated with scientists from the National Cancer Institute on numerous studies which have led to a much improved ability to predict the concentration of anticancer drugs in various parts of the body. This ability provides the basis for "engineering design" of potentially improved therapy.

Ovarian cancer offered an excellent opportunity to apply design concepts to cancer treatment. This disease usually spreads along the peritoneum, the membranes which line the abdominal cavity. A senior staff member of NCI proposed that the tumor might be effectively treated by instillation of a drug solution directly into the peritoneal cavity to bathe the tumor. We were able to synthesize a variety of information, including disposition studies in mice, peritoneal transport investigations in rats, and data from peritoneal dialysis of kidney patients. It appeared that many cancer drugs would be absorbed much more slowly across the peritoneum than they are eliminated from the body, thus exposing the tumor to a high drug concentration while limiting exposure of sensitive normal tissues.

This concept has been confirmed by early clinical trials in which approximately a 30-fold concentration difference was obtained between peritoneal and blood concentrations for one drug and 300-fold for another. These clinical trials represent the first demonstration of the validity of engineering design calculations in guiding therapy and the first example of quantitative *a priori* prediction of potentially exploitable concentration differences in the application of cancer drugs.

Measuring Physiological Parameters *in vivo*

Physical measurements of color, pH and temperature arising from experimental stresses applied by the bio-scientist to the living systems form the bulk of the scientific data from which hypotheses are developed leading to new insights into the functioning of those systems. The measurement of such physical changes, while generally quite simple in theory and in previous art, has become most difficult in application. As finer and more subtle measurements must be made without producing undesirable side effects in the living test system, sophisticated measuring instruments become of paramount importance. To a great extent, biomedical science has reached the point where advanced instrumentation must precede advanced research knowledge acquisition.

In order to provide such instrumentation and advanced measuring systems, many engineering skills may need to be integrated: general mechanical engineering, mathematical analysis, optics, fluid mechanics, chemistry and the like.

An example drawn from our work relates to *in vivo* measurement of important physiological quantities. Optical instrumentation can provide measurement of small increments of change in such parameters as color and fluorescence. These are used as indicators of biological phenomena such as pH, reagent concentrations and flow rates. Until recently, the use of optical measurement techniques in living systems has been restricted by the physical volume of the instrumentation components—for example, the light sources and sensors. The use of optical fibers permits convenient separation of these components from the living system, and many novel techniques can now be used for chronic measurements.

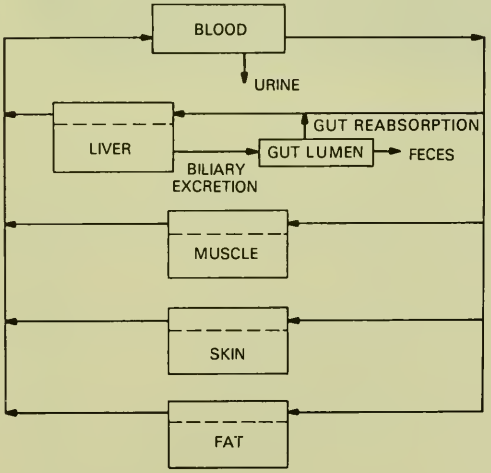
Fiber optics are thin, hair-like strands of specially treated glass or plastic which conduct light—much as a pipe carries water. A typical fiber optic probe consists of two such fibers several meters long. A light source illuminates the outer end of one fiber, and a light sensor is placed at the outer end of the other. The other end of the probe, with the fibers adjacent, is implanted in a test animal in a relatively noninvasive manner. The light sensor and light source are thus optically coupled to each other via the animal. The source fiber locally illuminates tissues as the sensor fiber provides a "view."

In one project, fiber optic probes measure blood flow in highly localized regions of tumor in laboratory rats. Fluorescein, a fluorescent dye, is injected into the blood streams of the rats and is detected as it slowly diffuses into the tumor tissues. A simple pharmacokinetic model allows the blood-flow-per-unit-volume to be determined from the relationship of the buildup of fluorescence-versus-time. Use of multiple pairs of fibers initially implanted in the animal along with fragments of tumor allows the blood flow in localized regions of the tumor to be studied as the tumor develops.

Studies of capillary permeability can be performed by using fluorescein which is bound to large molecules, such as dextrans. In this instance, the fluorescence buildup is influenced by the rate at which fluorescein leaves the capillaries. A more complex pharmacokinetic model thus enables the capillary permeability to be determined from the fluorescence buildup. The chronic *in vivo* technique enables the direct assessment of the effects of drug interventions on permeabilities.

In still another project, the fiber optic technique is being explored for the measurement of tissue uptake of substances having distinctive fluorescences, such as the chemotherapeutic agent adriamycin. Use of laser light sources greatly enhances the sensitivity, a requirement for substances which do not fluoresce strongly. In these studies, the optic probes are encased in small hypodermic needles and implanted in various organs of anesthetized animals.

By appropriately treating the ends of the optic fibers, a variety of physiologic measurements can be made. For example, a miniature pH sensor has been developed, based upon color changes in dyes at its tip. Use of plastic fibers results in a probe which is far smaller and more rugged than existing units, and consequently more suitable for metabolism studies in humans. Another probe for sensing the partial pressure of oxygen is currently under development. Other areas for future investigation include measurements of variation in local blood volume and the intrinsic fluorescent biochemical indicators associated with metabolism.



'Smart' Instruments

Almost from the beginning of electronic science there have been attempts to apply the full power of electronic technology to biomedical research. In recent years computational devices have been built into biomedical instruments in order to carry out many of the cognitive functions that were formerly the province of the human operator—for example, computation of simple arithmetic functions, calibrations, and scale conversion.

Microprocessor-based smart instruments and a logical extension, "smart" instrument systems, constitute a field of particular interest and importance. Illustrative of the smart instruments whose development BEIB completed this year is a precision temperature-measuring system in which the microprocessor holds the thermistor excitation power constant, despite change in resistance. This minimizes self-heating error; provides automatic correction for thermo-electric EMF's and amplifier offset voltages; calculates resistance from current and voltage measurements; solves an equation to determine temperature; and controls data acquisition, display, and recording. Two instruments—for use with mass spectrometers—provide functions such as: scan initiation, based on ion current; temperature measurement; peak integration; background correction; and peak-area-ratio calculation.

While these applications benefit from the compactness, speed, and power of the microprocessor, they do not realize one of the main advantages leading to the commercial success of the microprocessor: namely, cost savings possible when a system is mass produced with replicable software. Our experience and that of the electronics industry shows that software development for one-of-a-kind microprocessor-based systems has become a substantial (if not the major) cost. Accordingly, we are also pursuing an alternate approach in which the calculating capability resides in a programmable calculator interconnected with a variety of measurement and control devices. Starting with a programmable calculator and a few digital voltmeters about five years ago, we have proceeded to more powerful calculators and a considerable variety of compatible instrumentation. The great advantage of this approach is that any number of devices can be interconnected by simply plugging in standard cables, with no engineering development effort whatsoever. An industry-wide interconnection standard has made this possible. Another advantage is that software development is much easier, conserving our limited resources and making it feasible for the end user to make changes and extensions himself.

Certain blood disorders impair the ability of the red blood cells to transport oxygen to the tissue. A method of characterizing the condition of the red blood cell is to obtain and analyze the hemoglobin-oxygen equilibrium curve. A computer-based, automated method was developed which provides this important information to the investigator. The data can be obtained on samples of whole blood or on samples of hemoglobin solutions heretofore not possible by available methods. Blood samples are not damaged by this method and are available for further testing. Our engineers have assembled several other systems, including one for studies in exercise physiology.

If a patient is studied during controlled exercise testing, it is possible to use non-invasive methods to assess his ability to deliver oxygen to his tissues in response to the demand imposed by the work level. A computerized, exercise, stress-test facility has been built which analyzes respiratory flow and pressure along with oxygen and carbon dioxide concentrations. Measurements and computations are performed on a breath-by-breath basis. Using this approach, the clinician can detect the patient's anaerobic threshold by

observing the slope of a curve of respiratory quotient plotted against work rate. With this simple yet powerful technique the patient's condition can be followed carefully. The test takes ten minutes to run and is fully automated, requiring only one person to operate. The data are presented to the operator in real time and are available in hard copy form, following the completion of the test.

The stress-test device, using a programmable calculator, has led to a very interesting interaction with the microprocessor approach. By starting with the programmable calculator, the system became operable very quickly, thus facilitating development of system function requirements. But, the success of the system led to the addition of more and more functions, until the input/output speed-capability and memory capacity were overtaxed. At that point we developed a microprocessor-based system of greater capacity. This development was greatly facilitated by the refinement of specifications achieved with the first system, plus the fact that most of the original software could be reused by simply translating from one programming language to another.

As these various illustrations indicate, the skills of physical scientists and engineers are a rich resource for furthering the acquisition of biomedical knowledge.

Veterinary Resources Branch
Robert A. Whitney, Jr., D.V.M., Chief

Veterinary Resources Branch

Projects carried out by the Veterinary Resources Branch (VRB) during the year included development of a number of new animal models, research in diseases of laboratory animals, and extensive collaborative research with intramural investigators from most of the NIH Institutes.

The Branch produced 330,000 rodents, 1,000 purebred foxhounds, 550 rhesus monkeys, 105 goats, small numbers of inbred miniature swine, burros, and several species of primates. Purchased rodents and rabbits increased slightly from 630,000 last year to 645,000 this year. Prior to the Bangladesh ban on exporting rhesus monkeys, 1,860 were acquired and quarantined. Small numbers of other primates, carnivores, ungulates, and fowl were procured.

Major renovations were completed on the genetic monitoring, nutrition, and animal disease facilities in Building 14E, allowing the Branch to improve the quantity and quality of laboratory services to NIH investigators. The expansion of plasmapheresis services permitted the supply of large quantities of plasma from domestic livestock without increasing the number of animals used. Automated processing equipment permits the collection of large volumes of plasma with the cellular components of the blood being returned to the donors.

Monitoring of research animals for genetic type and microbiological contamination increased during the year. These quality assurance programs are becoming more and more sophisticated. VRB continues to furnish NIH investigators with the information and assistance required to solve problems relating to animal experimentation, health, nutrition, care, and husbandry.

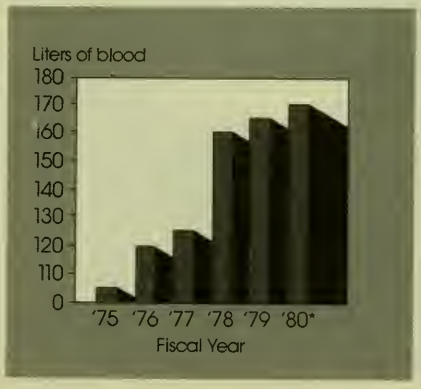
FY 1979 Activities

Animal Center Section—Larger species of laboratory animals such as primates, farm animals, carnivores (dogs and cats), defined foxhounds, swine, goats, and monkeys are produced and maintained by the section. Farm animal populations and services of the Ungulate Unit were increased. Foxhound production remained high; more emphasis was placed on producing well socialized animals and the use of dog pastures.

No foreign-source rhesus monkeys have been received for quarantine since January. Importation of rhesus monkeys from countries of origin has been erratic since April 1978 when India placed an embargo on exports. Monkeys were received from Bangladesh between September 1978 and January 1979, but this supply was terminated because of a dispute between the government of Bangladesh and the exporter. Consequently, facilities previously devoted to quarantining monkeys are being used to hold replacement breeders for breeding contracts and for long-term research primate holding. Facilities are also being renovated to maintain, hold, and breed small exotic primate species.

Unless foreign sources resume exportations, rhesus monkeys will be available only from the primate recycle program and the Branch's contract production colonies. These rhesus monkey colonies are progressing satisfactorily, and production levels would be adequate to supply current NIH intramural requirements. However, virtually all these monkeys are now being issued to the Food and Drug Administration's Bureau of Biologics for use in Federally mandated polio vaccine safety testing programs.

Ungulate Blood Issues



*Projected

The herd of inbred miniature swine bred and maintained for the National Cancer Institute has increased to 200 head. It will be maintained at this size, and provide sufficient progeny for histocomatibility and transplantation studies.

NIH research demands for behaviorally defined dogs have increased, and greater efforts have been made to provide well socialized foxhounds. The socialization program requires extensive contact between the dogs and their handlers. Overall requests for dogs has decreased during the past five years while production from the foxhound breeding colony has increased to about 1,000. If this trend continues, it will not be necessary to purchase dogs from commercial sources in 1980 and beyond. The average age of dogs required for research has gone up from 6 months to 12 months in the last five years. Demands for canine blood, at the same time, have decreased and the donor colony has been reduced accordingly.

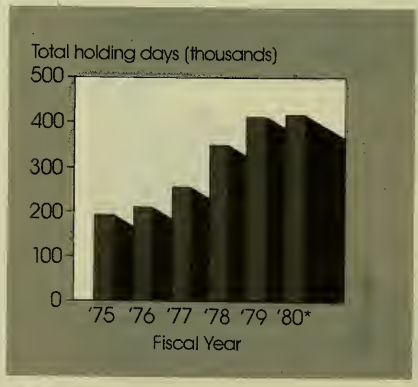
Comparative Pathology Section—This section is concerned with the study of naturally-occurring diseases of laboratory animals produced, quarantined, or utilized in biomedical research at the National Institutes of Health. It also assures the genetic quality of NIH animals, which are issued worldwide as a function of one of the World Health Organization's Collaborating Centers for Defined Laboratory Animals. The animal disease diagnostic and monitoring crobiology, and animal disease investigation services. Staff pathologists, microbiologists, and clinicians aid in control and elimination of disease in NIH animal colonies. Disease problems in a wide variety of animals are dealt with in conventional, germfree, and barrier-sustained colonies. Monitoring for many microbial agents and parasites is performed routinely.

The number of autopsies approached approximately 37 percent fewer than in FY 1978 and 1977. This decrease appears to have been caused by a variety of factors. Two that may have a permanent effect are the decreasing size of the Branch's rodent colonies and the diminished role of importation and quarantine activities in the supply of primates. Factors of more variable effect include the absence of major disease outbreaks this year and the temporary loss of clinical veterinary services at the Animal Center. Although the number of accessions decreased, the amount of work in connection with autopsies increased greatly because many more autopsies are being done for NIH investigators on animals suffering from a wide variety of problems. There are many infectious disease problems in the animal facilities of the BID's as a result of pooling animals from diverse sources.

The Animal Disease Investigation Service responded to 382 calls for assistance from the Institutes, an increase of 45 percent over FY 1978. At least part of the reason for the increase is that veterinarians in several Institutes have begun to act as arms of the ADI Service and to use it for laboratory assistance, especially in pathology and bacteriology.

Monitoring the genetic integrity of inbred mice is accomplished by testing for groups (profiles) of characteristics (markers) which identify the genetic constitutions of each strain. The profiles consist of morphological, immunological, and biochemical markers of 31 loci on 14 of the 19 mouse autosomes. The profiles

Long-Term Primate Research Holding



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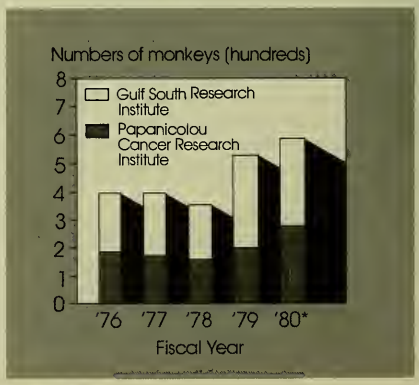
Rhesus Contract Breeding Colony Production



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also are used in investigations of suspected genetic contamination in animals in NIH laboratories. Research is aimed at refining and developing new marker systems and establishing profiles for use in monitoring additional animal genera. The set of genetic profiles for the inbred mouse colony was completed and partial monitoring of selected strains initiated.

New computer systems were designed and programmed for data analysis that will permit differentiation of strains of mice by both genotype and phenotype. A new program is being developed to computerize the breeding records and disposition of the animals. The Institutes made 36 requests to investigate genetic problems in animals and cell cultures.

Small Animal Section—This section breeds rodents and rabbits, including those characterized genetically and microbiologically. Care is taken to maintain the genetic integrity of inbred strains and minimize the inbreeding of random-bred stocks. Germfree and specific pathogen-free rodents are produced for intramural research programs and as replacements to enhance breeding and genetic colonies. Contractors produce rodents and rabbits to augment in-house production. These are delivered directly to NIH investigators. Quality control of these species is maintained through strict contract specifications and monitoring of the producers' facilities and operations by Branch staff members. The section holds germfree rodents for varying periods of observation while under test by investigators. Provision is made for physiological sampling and collection of specimens. The professional staff consists of specialists in laboratory animal medicine, epidemiology, nutrition, genetics, and animal husbandry. All efforts are oriented toward improving the section's programs by gaining new knowledge through research and assuring the health and genetic quality of procured and produced animals.

Approximately 329,000 rodents and rabbits produced within VRB were issued for intramural research, which is a slight decrease from the previous year. This represents a continuing trend resulting from contracting procurement activities.

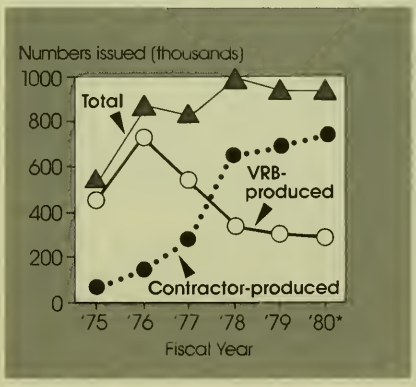
Total purchases of rodents and rabbits from contractors increased from 630,000 in FY 1978 to approximately 650,000 in FY 1979. Since there were no new contracts established, the increase represents a higher utilization of contract animals by NIH investigators.

The number of germfree isolators available for research holding was increased from 12 to 20. Collaborative efforts to cesarean derive and maintain germfree swine were successfully completed. Numerous hysterectomies were performed to provide rodents for the genetic resource and for investigators and contractors. The noninbred guinea pig colony located in the barrier unit will be phased out. Guinea pigs apparently require intestinal flora that is not of the types presently administered to animals entering the barrier.

The BALB/c mouse expansion colony was reestablished after resolving a problem with genetic contamination. In addition, the cotton rat colony was greatly expanded to meet the demand for mothers with litters and weanlings. The NIH Genetic Resource is designated by the World Health Organization as a Collaborating Center for Defined Laboratory Animals and as an International Nude Mouse Reference Center by the International Committee on Laboratory Animals. It contains approximately 240 closed breeding groups of the common as well as exotic species of small animals. Breeding nuclei from the genetic resource are supplied not only to intramural investigators but also to the international biomedical research community since many of the stocks, strains, and substrains are not available elsewhere. The breeding stock issued serves to support inhouse as well as contract production on a continuing basis.

The composition of the Resource remained relatively stable. One mouse mutant (pygmy) and one rat congenic (RCS-c) were added, three mouse strains (NB/N, BDL/N, and SPM/N) and one rat strain (CAS/N) were eliminated. The demand for introductions into the Resource has led to a substantial backlog. Presently, there are eight groups of mice, plus an equal number of rats awaiting quarantine.

Total Rodents and Rabbits Issued



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The Branch obtains or develops new animal models to meet previously unfilled research needs. Seven of 23 mouse congenics under development are formally complete; an additional three more require one more generation of crosses. The X-linked *Xid* gene affecting the maturation of B-lymphocytes is being introduced into 16 inbred mouse strains. A major effort is also underway to develop a series of immunodeficient mouse models and controls, including mice with normal T and B cell function; normal T and defective B; normal B and defective T; and defective B and T systems. Other congenic development projects involve the motheaten (*me*), dwarf (*dw*), and wobbler (*wr*) genes in mice and diabetes insipidus (*di*), jaundice (*j*), and corpulent (*cp*) genes in rats.

Generally, the health status of the rodent and rabbit colonies was good; no major disease outbreaks occurred. Antibody titers to Sendai virus disappeared from all of the guinea pig strains. All VRB colonies are now free of this ubiquitous virus. Cutaneous staphylococcosis continued to be a problem in some strains of nude mice. Studies have shown that the causative agent is not carried by personnel but that it is widespread within the barrier. Only certain strains of athymic (immunodeficient) mice are affected, and intact mice have never been observed with lesions.

The quality assurance program for animal feeds used at the NIH was reviewed and feed assay requirements were modified. Assays are now required for nine potential chemical contaminant concentrations in diet samples collected from each batch of diet manufactured under NIH feed contracts. Following a published report indicating the NIH open formula diet was contaminated with nitrosamines, contract arrangements were made for assays of this carcinogen to be performed by a university laboratory. Preliminary data indicate that, while fish meal, a dietary ingredient, may contain substantial amounts of nitrosamines, a large percentage of it is volatilized during the manufacturing procedures. During FY 1979, diets for all animal colonies maintained by the Small Animal Section were changed to existing open formula diets. The cost of the open formula diets is approximately 12 percent less than for comparable commercial diets. On an NIH-wide basis, this would result in a savings of over $50,000 for animal feed.

Provision of services to NIH investigators and the domestic and foreign research communities continues to be the most time-consuming activity for the nutrition program. Numerous investigators have expressed concern about the general quality of laboratory animal feeds and the concentrations of various chemical contaminants. In this regard, first draft copies of nutritional standards for studies conducted by the National Toxicology Program and the Environmental Protection Agency were prepared.

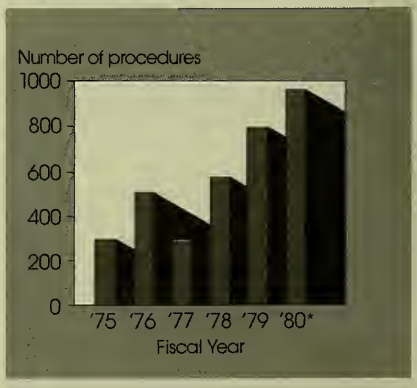
Ascorbic acid concentrations in guinea pig and non-human primate diets remain a major factor affecting the quality of NIH animal diets. A 25 percent increase in the amount of ascorbic acid added to these diets is being required to compensate for losses known to occur during periods of high temperature and humidity.

There has been considerable concern regarding the causes of a "wasting syndrome" in marmosets throughout the research community. New open formula diets are being evaluated with the objective of determining the quantitative nutrient requirements of these species. Efforts are also underway to formulate primate diets with ingredients that are available in specific areas of South America.

Nutrition, animal disease research, and genetic monitoring programs continued operating at suboptimal levels because of an 18-month delay in renovating Building 14E. The facility is scheduled to be available for use in early FY 1980.

Veterinary Medicine and Surgery Section—This section provides a variety of services to the NIH intramural research programs, including veterinary advice, assistance in surgery, radiology, and health care. It manages central NIH facilities for surgery and postoperative care and long-term research holding for

Surgical Procedures



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dogs, cats, livestock, and nonhuman primates. The section also manages primate breeding colonies to meet NIH needs for timed-pregnant macaques.

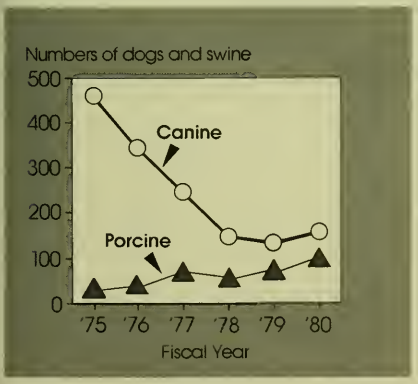
Although dogs continue to be major research animal models for many human disorders, miniature swine are becoming more widely used for this purpose. A decline in canine holding coincides with increased use of swine, which need more space.

Primate holding has consistently increased over the past few years. This has come about with completion of various stages of renovations to the centralized holding facility. The primate recycle program began early in 1977 to help offset the limited availability of wild-caught rhesus monkeys. The program is expected to continue at its present level of about 100 animals.

Breeding of timed-pregnant primates is conducted at a Branch and a contract production colony, each providing an approximately equal number of issues. Utilization of this resource is increasing and a total production now exceeds 200 animals.

Increases in surgical procedures over recent years reflect the availability of improved and expanded facilities. The staff provides complete surgical services to accommodate research needs and assists in developing new surgical models of human disease. Studies performed during FY 1979 involved mice, guinea pigs, dogs, primates, sheep, and miniature swine. Collaborative research between the section and various Institute programs has increased steadily over the past few years. Investigators are utilizing available professional and technical services to accomplish increasingly sophisticated medical and surgical research.

Long-term Canine and Porcine Research Holding



FY 1980 Outlook

Animal Center Section—Additions are planned to Buildings 100 and 102 to accommodate the increasing numbers of livestock required by NIH research activities and to provide an improved breeding facility for foxhounds. Additional dog pastures are to be constructed, and limited facilities for housing groups of monkeys in outdoor pens are projected.

Future primate supply activities for NIH and other agencies will rely upon expansion of contract breeding operations, because sources for wild-caught monkeys have not been dependable. The primate program at the Animal Center will become more involved with the breeding of exotic species, long-term holding, research, and development.

An automatic data processing system is being developed that will cover all Animal Center activities. A pole barn will be constructed to house sheep at the Animal Center. Three Springs Farm will be developed further with an additional pole barn, fencing, and the provision of tenant housing.

Comparative Pathology Section—The feasibility of initiating inhouse serologic testing programs for murine viruses is being explored. Such a program is needed to ensure fast, accurate results for the monitoring program, provide the experience base for improving and developing new tests, and to permit collaboration internationally with other laboratories interested in expanding methods for assuring the quality of laboratory animals.

A cytogenetics program was started in order to incorporate chromosome studies into the genetic monitoring program. These studies are important in the evaluation of mutant strains and unusual hybrids. Work has been focused on the establishment of protocols and techniques for chromosome preparations from mice, guinea pigs, and rabbits.

Small Animal Section—Renovation of Building 14F is scheduled for FY 1980. It will be converted to a barrier facility to expand the capacity of the Genetic Resource. Renovations will require an increase in contracting activities relative to the production colonies currently located in the building.

An embryo banking program will be developed to permit preservation of rodent strains of potential value to the biomedical research community.

The NIH Rodent Catalogue is being revised and will be published in FY 1980.

The initial purchase of hardware and software to implement a computer assisted colony management program should occur in the near future. Completion of the program will require several years and is scheduled to coincide with renovations to the facilities.

Environmental Services
Rudolf G. Wanner, M.D., Acting Chief

Environmental Safety Branch

Responsibility for the NIH Environmental Safety Program is shared by the Environmental Safety and Radiation Safety Branches. The Environmental Safety Branch's main areas of concern are the handling and disposal of potentially hazardous nonradioactive substances; the testing, maintenance and decontamination of laboratory equipment; industrial hygiene, sanitation, and occupational health and safety. The Branch also provides media and glassware to researchers.

Much of the staff's time during the year was devoted to upgrading waste disposal procedures to comply with the Federal Resource Conservation and Recovery Act and new regulations imposed by the State of Maryland. The State now requires complete reporting data on all designated hazardous substances in use at NIH along with manifesting for all chemicals leaving NIH for disposal.

Publication of the revised version of the NIH *Guidelines for Research Involving Recombinant DNA Molecules* necessitated the reevaluation of 60 current Intramural Memoranda of Understanding and Agreement (IMUA) by the NIH Biosafety Committee. Twenty-two were exempted and the remainder were assigned lower levels of biological and physical containment. The lowering of the physical containment level brought a large increase in the number of submitted IMUAs because investigators could work at the lower P1 and P2 levels on research that was considered P3 or P4 under the old *Guidelines*.

In addition, the number of amendments to existing IMUAs has steadily increased because the Director, NIH, has approved recommendations of the Recombinant DNA Advisory Committee (RAC) for the certification of new host-vector systems, new combinations of DNA molecules, equivalency of physical and biological containment levels (P2-EK2 and P3-EK1 are equivalent), and other major changes in the revised *Guidelines*. The chief of the Branch's Biological Control Section has been appointed the biological safety officer and is a member of the NIH Biosafety Committee while the microbiologist in the section has become the executive secretary of the committee.

Biosafety and Contamination Control

The Branch provides testing, maintenance, and decontamination services for biological containment equipment and systems at NIH facilities in the Washington, D.C., metropolitan area and Baltimore, Maryland. This service under contract covers Class I, II, and III biological safety cabinets, laminar flow clean air cabinets, animal care high efficiency particulate air (HEPA) filtered modules, and other units and systems containing HEPA filters. Approximately 1200 units were tested and serviced.

The National Sanitation Foundation, Ann Arbor, Michigan, is evaluating the premise that if the largest size of a series of Class II biohazard cabinets passes its biological and physical tests, and other models on the series pass only the physical tests at the manufacturer's plant, then all the cabinets in the series are acceptable under the Foundation's standards. Preliminary results indicate the premise is correct.

Building 41T is being renovated for the conduct of recombinant DNA research at the P4 level of physical containment. Building 37's balance design will be changed to provide a high static pressure to compensate for the high pressure drop across the HEPA filters in the Class II, Type B cabinets. In January 1979, the assessed risk of the research being conducted in the Mobile Containment Laboratory (MCL) was downgraded from P4 to P2 level according to the revised *Guidelines*. However, the Office of Specialized Research and Facilities, National Institute of Allergy and Infectious Diseases, requested the MCL remain "P4 ready" should there be a need for it. Currently the MCL is being used for P3 research.

Industrial Hygiene, Sanitation and Sanitary Engineering

Preliminary testing of waste chemical destructors was completed this year. The results were rather encouraging, indicating this option should be pursued further. A unit may be procured to analyze chemicals on a case-by-case basis to establish a level of confidence in the destructor's capabilities and to determine the range of chemicals acceptable for incineration.

Animal facility surveys and evaluations were made in response to several institute requests to bring these facilities into compliance with the American Association for the Accreditation of Laboratory Animal Care certification criteria.

Personnel awareness of occupational and environmental hazards increased the industrial hygenists' workload significantly. Problems ranged from odor complaints to concern about asbestos exposure during renovation and the cleanup of highly hazardous chemical spills. The rental buildings, in particular, were a major factor in this workload increase. The number of occupational health evaluations performed by ESB staff continues to increase. These evaluations often involve direct measurements of physical or chemical agents using portable instruments or field sampling with analyses performed by an outside laboratory under contract.

Close contact is maintained with the Occupational Medical Service staff through regular meetings and contacts. Industrial hygenists regularly evaluate physical agents in the NIH environment. They include noise evaluations, laser hazards and controls, microwaves, and ultraviolet light evaluations. All 800 chemical hoods at NIH are surveyed annually by contract. In addition, specific hoods are surveyed by Branch personnel throughout the year.

Safety Management

At the beginning of 1979 a monthly safety orientation for all visiting scientists was established. The 2½ hour presentation represents input from all safety functions and, based on general comments, is considered to be an effective technique which has been well received. Several communication tools were produced during the year and additional ones are now in varying stages of completion. A project identified last year, acetylene use, was brought somewhat nearer to completion with the installation of the equipment.

A significant amount of time was devoted to the investigation and subsequent report of the serious fire in the Clinical Center. Factors which influenced fire

spread and response effectiveness have been identified. The Branch also has responded to requests for interpretation exceptions regarding compliance with corridor safety policy as a result of this fire.

Hospital Environmental Control

A biological quality control program has been developed for all operational Clinical Center sterilizers to meet Joint Commission on Accreditation of Hospital requirements. More than 1500 tests have been performed.

Environmental Studies

A newly developed analytical procedure for assaying endotoxins (pyrogens) is being evaluated. Pyrogens are high molecular Lipopolysaccarides that are produced by gram-negative bacteria growing in water and other media which produce fever or cause inflammation when injected intraveneously. Their presence in parenteral solutions is detected by biological methods using rabbits as test animals or by using "The Limulus Amebocyte Lysate Test." The method being developed by the Branch should be simpler and more sensitive. It is a simple chemical test utilizing UV absorption as a means of detecting and quantitatively analyzing pyrogens in aqueous solutions. The method is being studied to increase its scope and the detection limit of the test from two parts per billion to less than 0.1 part per billion.

The National Biomedical Containment Laboratory, Frederick, Maryland, is being renovated to provide a large moderate and high containment facility satisfying the certification requirements for P3 and P4 recombinant DNA research.

Media and Glassware Production

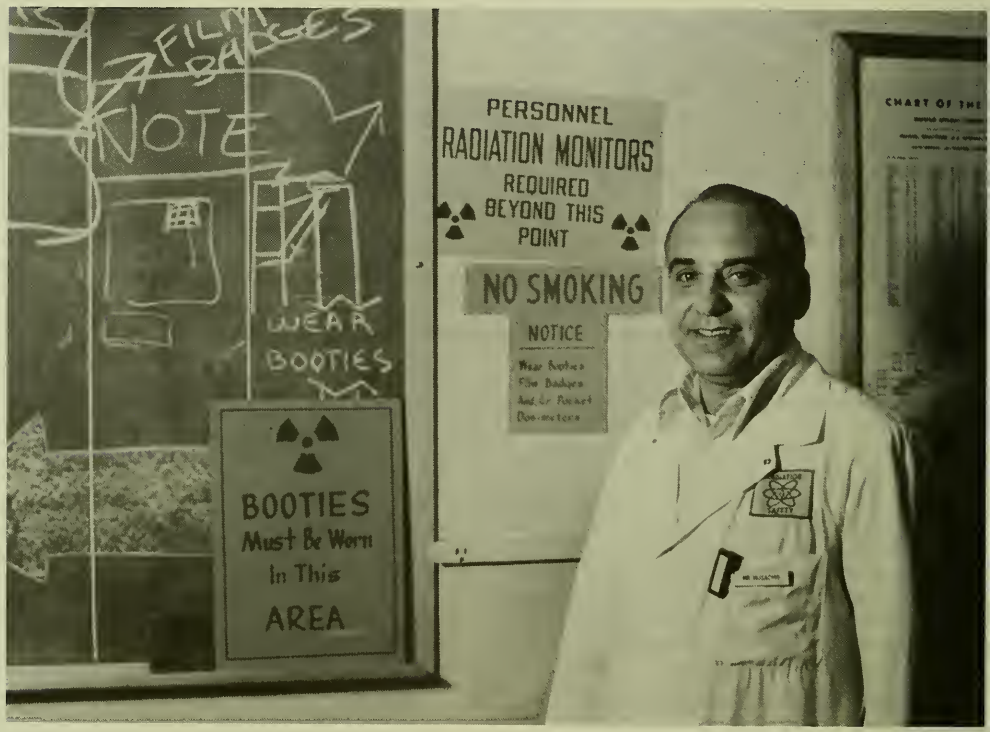
About 15,000 requisitions were processed for all media types with a total volume of 164,000 liters of media produced—a 5 percent increase over FY 1978. Of this total 80,000 liters were tissue culture media and 84,000 liters were bacteriologic media. Issues of glassware totalled 5,250,000 pieces, a decrease of 7 percent.

An automated petri dish handling system which fills the dishes with agar medium and quickly gels it has been installed. Automated labeling systems for both petri dishes and culture tubes are expected to be operational at the beginning of the new fiscal year in response to a requirement by Clinical Pathology. This equipment is expected to lead to a shelf-life dating system for most media types.

Extensive renovations to the Media and Glassware space in the Clinical Center are scheduled to begin early in FY 1980. The work will be phased to permit the uninterrupted production of both media and glassware.

International Activities

Consultant services continued to be provided to the World Health Organization's Special Programme on Safety Measures in Microbiology. Branch staff participated in the working groups on laboratory safety elements and development of emergency services. In the course of this cooperative effort, the Branch Chief went in January on a 2-year assignment to Geneva, Switzerland, to coordinate the activities of the Special Programme.



Radiation Safety Branch
Michael Musachio, Chief

Radiation Safety Branch

The National Institutes of Health is authorized to procure and use radioactive materials on the Bethesda reservation under a Type A specific license of broad scope issued by the Radioisotopes Licensing Branch, Division of Materials and Fuel Cycle Facility Licensing, U.S. Nuclear Regulatory Commission. This license is contingent upon the existence of a radiation safety organization—a function fulfilled by the Radiation Safety Branch. In size and scope the NIH radiation safety program is one of the largest in the world, being exceeded by only a few of the National Laboratories operated by the U.S. Department of Energy.

Some sources of ionizing radiation are not covered by the NRC license. They include X-ray equipment, high-energy particle accelerators, and naturally occurring or accelerator-produced radionuclides. These sources are, however, controlled by an Executive Order relative to compliance with rules and regulations issued by the Occupational Safety and Health Administration of the U.S. Department of Labor; regulations of the Food and Drug Administration; and policy promulgated upon the recommendation of the NIH Radiation Committee.

The Radiation Safety Branch, under the direction of the NIH Radiation Safety Officer, is responsible for providing health physics services to the NIH intramural research community and assuring compliance with all applicable regulations and NIH radiation safety policy. The overall program philosophy is that radiation exposures and releases of radioactive materials to unrestricted areas be maintained as low as reasonably achievable.

Program Activities in FY 1979

Room 103 in Building 21 was renovated to prepare radiopharmaceuticals for positron emission tomography studies to be conducted by the Nuclear Medicine Department of the Clinical Center. Fluorine-18 for these studies will initially be supplied by the Naval Research Laboratory cyclotron facility.

A highly efficient and accurate counting method and instrumentation package was developed for the determination of the radioactive content of environmental samples (ash, water, air). This technique uses several automatic calibrating, counting, and data reduction programs to produce results and records. It also alerts managerial personnel of the need for corrective action if samples contain radioactivity above predetermined "action" levels. This system proved to be useful in the analysis of samples collected as a result of the Three Mile Island nuclear power plant incident.

The Branch introduced computerized inventory and bioassay data processing programs. They employ a keypunch ordering form and store bioassay data in computer records rather than on cardex file. Personnel film badge dosimetry records and radiation safety training records will also be an important part of this comprehensive data system.

No personnel exposures, releases of radioactive materials to unrestricted areas, or other radiation incidents occurred at NIH during the year which required reporting under Nuclear Regulatory Commission regulations.

Selected statistics for FY 1979 are compared with FY 1975 in the accompanying table.

Selected RSB Statistics FY 1975 vs. FY 1979

	FY-75	FY-79	Change
Radioactive Shipments	9,163	15,062	+ 64%
Activity Received (curies)	122	198	+ 62%
Value of Shipments (million dollars)	1.3	2.9	+123%
Radioactive Waste (55 gallon drums)	2,056	3,160	+ 55%
Laboratory Surveys	5,163	11,885	+130%
Personnel on Film Badges	1,945	3,551	+ 83%
Bioassays	1,260	4,528	+259%
Personnel	21	23	+ 10%

Library Branch
Mrs. Ruth C. Smith, Chief

Library Branch

Major advances in the area of on-line search capability for NIH investigators were made during this fiscal year.

First, the Reference and Bibliographic Services Section substantially increased its usage of the data bases of Bibliographic Retrieval Services, Inc. (BRS). From an average of a few searches per month, they now process well over 100. BRS provides access to such important data bases as BIOSIS *(Biological Abstracts),* CA Condensates *(Chemical Abstracts),* and *Psychological Abstracts.*

The Library acquired its second new on-line capability, the NIH-EPA Chemical Information System, supplementing MEDLINE. The newly added system is a network of chemical data bases, at the heart of which is the Structure and Nomenclature Search System used for substance identification.

The broad range of data bases provided by the Lockheed "Dialog" system became available in July. Over 60 data bases are included, among which Excerpta Medica and SCISEARCH *(Science Citation Index)* are of prime interest to NIH.

The Branch also participated in an experiment with the Lister Hill National Center for Biomedical Communication to evaluate a new hepatitis data base. Unlike the majority of data bases which provide only citations to the published literature, this one gives actual information and data that have been reviewed by a panel of experts. The hepatitis file is the first in a series of data bases being developed by Lister Hill National Center. The NIH Library also will be involved in the testing and evaluation of these files.

Located in the Clinical Center, the Library has available these other services to support NIH research: circulation of current literature, interlibrary loan, reference, translation, photocopying, and non-print media. The circulation system is automated.

During the year, a study was launched into the feasibility of expanding automation to other Library activities. The automation project is being conducted with the assistance of the Division's Management Analysis Office and the NIH Division of Computer Research and Technology. The Library's total automation requirements are being looked at along with systems that might be adapted to meet these requirements.

The Library Advisory Committee and various NIH investigators worked with the Branch staff to make more shelf space available for new acquisitions, yet assure that older materials will still be available. Accordingly, the years for the holdings of journals on the upper level were reduced to four plus the current year. Many pre-1930 titles were placed in storage and out-of-scope or ceased publications were discarded. Titles eligible for discard but for which requests were still being received were retained. Significant titles were purchased in microfilm format and new microfilm reader/printers were purchased.

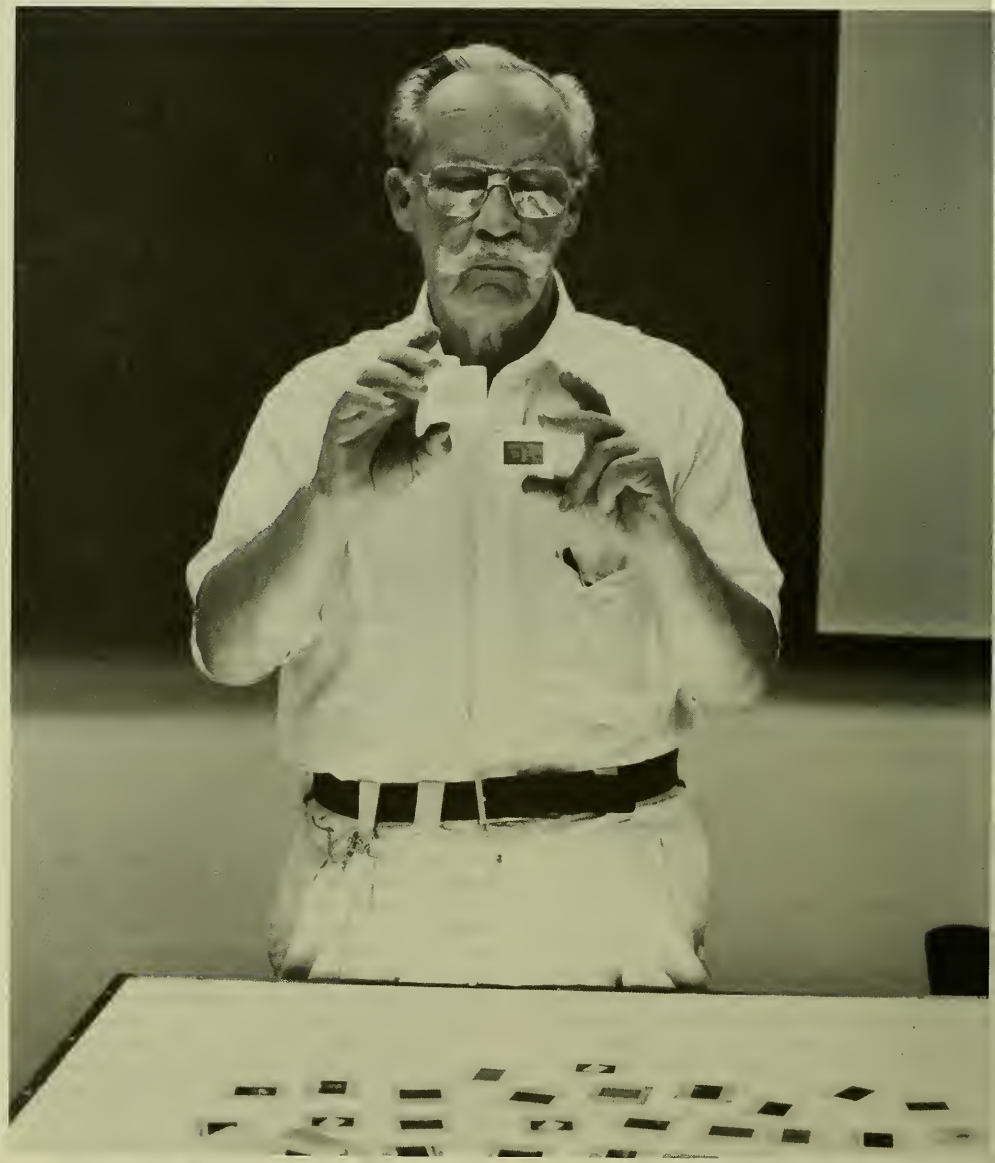
An allied project to weed out unserviceable monograph publications was completed during the year. Some 12,575 volumes and 102,400 cards were withdrawn, allowing the collection to be replenished and updated.

FY 1980 Plans

The direction of the Library automation project will be determined after thorough study of the report prepared by the Division of Computer Research and Technology. The initial emphasis may concentrate on an on-line catalog representing the entire collection. Such a catalog could form the basis for such future subsystems as acquisitions, updated circulation control, interlibrary loan, and journals control.

Space in the journals collection will remain a problem. More compact shelving will be installed on the upper level and only the current issue will be displayed. The space saved will be used to expand the shelving for the most recent journals. On the lower level, the only recourse will be to continue to replace hard copy with microfilm, since the Library is in a no-growth situation. The use of journal literature in microfilm or microfiche format is expected to increase.

The Clinical Center's modernization plans for the B-1 concourse and the subsequent expansion of other facilities into library space will disrupt the programs on that level. The principal areas affected will be the photocopy service, the nonprint media program, the mail and receiving area, the reading room, and the staff room. These programs and activities are expected to be relocated in space now occupied by the Photography Section, Medical Arts and Photography Branch.



Medical Arts and Photography Branch
Arthur F. Moore, Chief

Medical Arts and Photography Branch

Demand for the Branch's photographic, graphic arts, and other services increased by 30 percent in Fiscal Year 1979 over the previous year—a measure of the amount of new biomedical knowledge being generated by NIH investigators. Most of the Branch's work assists scientists in recording the results of their research and communicating it in published articles and papers.

The Branch's staff of 51 artists, photographers, and other specialists are highly skilled in meeting the needs of scientists for graphic presentations, still and motion picture photography, including photomacrography and photomicrography, and medical arts. Services also include the design and production of publications; the preparation of slides, vu-graphs, and other projected visual aids; animation artwork; technical, general, and medical illustrations; exhibit design; statistical drafting; display charts, and medical models.

The philosophy of the Branch is to provide high quality professional services competitive in cost with commercially obtainable services. The staff monitors graphic and photographic services procured by outside contract to assure quality standards are kept.

The heavier demand for finished artwork during the year was met by a corresponding increase in contract services and an acceleration in deliveries. Photographic services and graphic services are performed normally in five workdays. But 24-hour emergency service is available. Design work is turned out in 10 workdays; this time also may be reduced by the Branch staff in special cases.

Audiovisual Leadtimes

Adequate leadtimes are the key to producing quality audiovisual materials. Experience shows that many members of the NIH community fail to allow enough time for planning and production; errors often crop up in submitted raw data causing delays and higher costs. The Branch has extensive expertise in conversion of data into effective multimedia presentations. This counsel is readily available for all of the Branch's services and should be used earlier and with more frequency. Needless demands for rush work are an imposition on others who have scheduled their projects with proper leadtimes.

A graphic design manual prepared by the Branch is available to investigators to assist them in planning and producing desired visual communications. This publication is gaining wider acceptance and is helping to effect savings by establishing standards and reducing preliminary design problems.

FY 1979 Section Activities

Photography Section—Technological improvements were instituted in the areas of photomicrography, photomacrography, and photographic laboratory services. The improvements were accomplished by increased technical training of personnel and by replacing old equipment with advanced photographic tools. The section extensively employed outside vendor services from private photo firms in the Washington, D.C., area, in addition to in-house facilities, in order to keep pace with the ever increasing calls for photography services.

Design Graphics Section—The section possesses a nucleus of well-trained, extremely dedicated personnel. This enables the group to respond to requests for complex visual productions, which are continually mounting in numbers. The section had a productive year, augmenting output 30 percent with no increase in personnel and maintaining its usual high quality production. Requests for medical illustrations remained at a normal level throughout the year. Contracting was seldom used since few projects entailed short deadlines. Calls for medical models remained about the same as in FY 1978.

Motion Picture Section—Filming increased by 15 percent with several more formal productions completed than in the previous year.

FY 1980 Outlook

The Medical Arts and Photography Branch will pursue the development and implementation of a system to upgrade NIH visual communications. It will aim to improve, enlarge, and extend its services and will seek additional ways to acquaint the NIH community with its skills. The importance of early counsel and planning, for optimum service, will be emphasized.

☆U.S. GOVERNMENT PRINTING OFFICE: 1979 O— 630-860/8985 REGION 3

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH

DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT FY 1979

Dr. Murray Eden, Chief

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10001-11 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Chief	ChES BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	R. Jones	Oncologist	MB NCI
	A.M. Guarino	Chief	LT NCI
	R.J. Lutz	Chemical Engineer	BEIB DRS
	A.F. LeRoy	Chemical Engineer	BEIB DRS
	M.W. Anderson	Mathematician	BB NIEHS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	H.B. Matthews	Pharmacologist	PB NIEHS
	I.G. Sipes	Assistant Professor	Univ. of Arizona
	C.E. Myers	Oncologist	CPB NCI
	J.M. Collins	Guest Worker	BEIB DRS
	J.L. Speyer	Oncologist	MB NCI

COOPERATING UNITS (if any)

LCHPH-NCI; PB-NIEHS; AK-CU Program NIAMDD; M-NCI; EB-NIEHS; CPB-NCI.

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

CRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby improve chemotherapy, hemodialysis, and risk assessment.

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide rational basis for extrapolation of toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimization of cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of in vitro thermodynamic and kinetic data to in vivo cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physiocochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

(1) Ovarian cancer is being treated by intraperitoneal administration of anticancer drugs according to pharmacokinetic principles. Phase I clinical trials have been completed with methotrexate (MTX) and 5-fluorouracil (5-FU). The peritoneal MTX concentration could be maintained 18-36-fold higher than corresponding plasma concentrations, in good agreement with design predictions. Because of its rapid and extensive metabolism, mean 5-FU plasma concentrations were 300-fold less than corresponding peritoneal fluid concentrations. Toxicity to i.p. 5-FU showed a very steep concentration-response curve, possibly mediated in part by saturable elimination.

(2) 5-FU is being administered in large volumes intraperitoneally as a surgical adjuvant in the treatment of colon cancer. The purpose os to perfuse the portal system and provide relatively high concentrations of drug to any microscopic hepatic metastases.

(3) A preclinical toxicology study was designed for adriamycin administered i.p. in large volume to the rat. Repeated administration mimicked the expected clinical application and provided guidance on both early and delayed toxicity.

(4) Pharmacokinetics of 5-Fluorouracil in the rat are being investigated to provide information relevant to clinical studies utilizing intraperitoneal 5-FU, and to establish the data basa for rat-human pharmacokinetic modeling. Two types of experiments have been carried out: (1) Intraperitoneal and plasma 5-FU concentration-time profiles have been measured following instillation of 25 or 50 ml of drug solution into the peritoneum. An intriguing concentration-dependent peritoneal disappearance has been observed. (2) Total body clearance of 5-FU has been studies by measurement of arterial plasma levels during a continucous intravenous infusion of drug. Non-linear clearance has been detected.

(5) A physiological pharmacokinetic model has been developed for 2-amino-1,3,4-thiadiazole (ATDA) in the mouse, dog, and monkey. In all speices both ATDA and metabolites are eliminated in the urine. Kidney clearance of ATDA is significantly less than glomerular filtration rate indicating considerable reabsorption. The kidney clearance shows a 0.7-degree dependence on body weight. Saturable metabolism was inferred in the dog and monkey but not observed in the mouse at the dose reported. Quantitative differences in metabolism render predictability to humans uncertain.

Significance: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with considerable of pharmacodynamic and cytokinetic events. Continued clinical emphasis through support of intraperitoneal procedures and other measures to overcome drug resistance. Increased emphasis on research designed to investigate distribution and metabolism of environmental contaminants. Investigation of use of in vitro assays of chemical metabolism in conjunction with pharmacokinetic models for quantitative prediction of metabolism in vivo.

Publications:

Jones, R.B., Myers, C.E., Guarino, A.M., Dedrick, R.L., Hubbard, S.M., and DeVita, Jr., V.T.: High-volume intraperitoneal chemotherapy ("Belly Bath") for ovarian cancer; pharmacologic basis and early results. Cancer Chemother. Pharmacol. 1, 161-166, 1978.

LeRoy, A.F., Lutz, R.J., Dedrick, R.L., Litterst, C.L., and Guarino, A.M.: Pharmacokinetic study of cis-Dichlorodiammineplatinum (II) (DDP) in the beagle dog: Thermodynamic and kinetic behavior of DDP in a biologic melieu. Cancer Treatment Rep. 63: 59-71, 1979.

Myers, C., Jones, R., Londer, S., Brennan, M., Balow, J., Dedrick, R., Ozols, R., and DeVita, V. Pharmacology of high-dose methotrexate (MTX) administered via peritoneal dialysis (abstract). Proc. 14th Ann. Mtg. Am. Soc. Clin. Oncology 19: 390, 1978.

Speyer, J.L., Collins, J.M., Dedrick, R.L., Brennan, M.F., Londer, H., DeVita, Jr., V.T., and Myers, C.E. Phase I and pharmacological studies of intraperitoneal (I.P.) 5-Fluorouracil (5-FU). Proc. 15th Ann. Mtg. Am. Soc. Clin. Oncology (Abstract) 20: 1979 (In press).

Dedrick, R.L. Pharmacokinetics of Vinylidine Chloride (Letter). Environmental Health Perspectives (In Press).

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Pharmacokinetics of Halogenated Hydrocarbons. Ann. N.Y. Acad. Sci. (In Press).

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Pharmacokinetics of environmental contaminants in dynamics, exposure and hazard assessment of toxic chemicals in the environment. Ann Arbor Science Publishers (In Press).

Yang, K.H., Fung, W.P., Lutz, R.J., Dedrick, R.L., and Zaharko, D.S. In Vivo Transport of Methotrexate in Meirine Lewis Lung Tumor. J. Pharm. Sci. (In Press).

Dedrick, R.L., and Bischoff, K.B. Species similarities in pharmacokinetics. Proc. FASEB (In Press).

Lutz, R.J., Dedrick, R.L., and Zaharka, D.S. Physiological Pharmacokinetics: An In Vivo Approach to Membrane Transport. J. Pharmacol. Therap. (In Press).

Sikic, B.I., Collins, J.M., Mimnaugh, E.G., and Gram, T.E. Improved therapeutic index of bleomycin when administered by continuous infusion in mice. Cancer Treatment Rep. 62: 2011-2017, 1978.

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Physiological pharmacokinetic modeling of environmental agents. 71st Ann. Mtg., Am. Inst. Chem. Engrs. Paper No. 70C, 1978.

Himmelstein, K.J., and Lutz, R.J. A review of the applications of physiologically based pharmacokinetics. 71st Ann. Mtg., Am. Inst. Chem. Engrs. Paper No. 70a, 1978.

Collins, J.M. Comparative features of physiological and empirical (compartmental) pharmacokinetic models. 71st Ann. Mtg., Am. Inst. Chem. Engrs. Paper No. 70d, 1978.

Himmelstein, K.J. and Lutz, R.J. A Review of the Applications of Physiologically Based Pharmacokinetic Modeling. J. Pharmacokinetics and Biopharmaceutics, April, 1979. (In Press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10002-14 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB DRS
OTHER:	C.L. McIntosh	Senior Surgeon	SU NHLBI
	W.S. Pierce	Associate Professor	Penn. State Univ.
	J. Doppman	Radiologist	DR CC
	J. Wilkins	Physical Scientist	BEIB DRS

COOPERATING UNITS (if any)

SU-NHLBI; DR-CC; Pennsylvania State University

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared materials and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Prostheses such as artificial hearts, heart valves and catheters will be employed. Observations should include scanning electron microscopy (SEM), infrared spectroscopy, contact angle measurements, and energy dispersive X-ray analysis. Physical measurements will be made of tensile properties, flexural-fatigue resistance, electrical properties, hardness, density, coefficient of static and kinetic friction, hydrophilicity, and other surface and bulk properties.

Objectives: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic composition of the biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Observations include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis, and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studies in vitro in a test apparatus. Electronic implants are examined periodically in vivo for changes in threshold levels, corrosion, and tissue reactivity. In vitro studies of the aforementioned are designed to accelerate fatigue testing and methods of improvement through heat treatment of the metal components undergoing stress. Surfaces of catheters are modified using surface treatments of grafted polymers and copolymers to reduce drag through the blood vessels. These catheters are tested for burst strength, stiffness, tensile strength, and density. The basic composition is modified through compounding. Embolizing agents consisting of composites of polymers, ceramics, and metals are being devised for delivery through the catheter systems so as to block arteries and vessels in the treatment of lesions such as aneurysms and arteriovenous malformations.

Major Findings: Additional forms and compositions of embolizing agents implanted in cats and monkeys have proven to be unsatisfactory due to localized tissue reactivity.

A technique for co-injection molding of polyurethane provided an improved design concept for the artificial heart valve under development.

A new form of hydrogel coating has provided reduced drag of the surface of polyurethane catheters moving within larger catheters.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, indwelling catheters, and subcutaneous uses.

Proposed Course: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, determine their interactions with blood and subcutaneous tissue to facilitate development of better surgical implants.

Publications:

Boretos, J.W. Unitized tri-leaflet heart valve. Proc. 11th International Biomat. Symp., Clemson, SC, April 28-May 1, 1979.

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 RS 10007-05 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	B.A. Vern	Clinical Associate	CNB NINCDS
	W.C. Whitehouse	Electronics Technician	ADM CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS; AB-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

[ ] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [X] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism, as indicated by the fluorescence of nicotinamide adenine dinucleotide (NADH) and oxygen consumption, was assessed to investigate potassium ion kinetics in the cat brain. Research was conducted to determine if the potassium clearance process is active or passive after activation of the cortex. Investigations were also conducted to determine the applicability of the NADH fluorescence technique to exposed myocardium. Active work on this project was completed before September 30, 1977; two papers were published subsequently.

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. To compensate for blood volume changes within the field of interest, we developed and used a television fluorometer employing fluorescein dye as a reference. The technique, initially used for study of cat brain, was also applied successfully to exposed myocardium.

A potassium-sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated oxygen consumption is proportional to the arterial-venous oxygen concentration difference multiplied by the flow rate.

For the Q_{10} experiments, the exposed cat hippocampus temperature was either elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: The NADH dynamics observed in the myocardium are similar to those observed in the cortex.

Blood volume in transiently ischemic myocardial tissue may increase due to relaxed muscle tone.

Fluorescein fluorescence was found to be an excellent indicator of myocardial perfusion.

Agreement was found between an analytical model for potassium clearance and experimentally determined potassium kinetics. This agreement provided further evidence of the active clearance process previously suggested by Q_{10} measurements and the slowing of potassium clearance during periods of hypotension.

Publications:

Vern, B., Schuette, W., and Thibault, L.: (K^+) clearance in the cortex. A new analytical model. J. Neurophysiol. 40: 1015-1023, 1977.

Lewis, D.V., Mutsuga, N., Schuette, W.H., and Van Buren, J.: Potassium clearance and reactive gliosis in the alumina gel lesion. Epilepsia 18: 499-505, 1977.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10011-05 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Electrical Safety Program for Clinical Center Patients and Patient Care and Treatment Areas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Corsey	Electronic Engineer	BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	C. Strong	Environ. Services Officer	CC
	T. Johnson	Administrative Officer	CC
	J. Bucolo	Electronic Technician	BEIB DRS
	W. Connoley	Super. Electronic Tech.	BEIB DRS

COOPERATING UNITS (if any)

ADM-CC; SMS-BEIB

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0		1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The electrical safety program assures a safe electrical environment for Clinical Center patients by performing the following functions: ensure Clinical Center compliance with standards of the Joint Commission on Hospital Accreditation; test on a regular basis all electrical clinical equipment; train CC staff members in electrical safety and grounding; inspect new construction and renovation; design and modify test equipment; gather and analyze data on electrical shocks and burns; participate in activities of the Clinical Center Safety Committee, counsel medical and nursing staff on new equipment purchases; participate in formulation of national electrical safety standards; modify existing clinical equipment to meet current electrical safety standards; and establish Clinical Center electrical safety standards.

Objectives: To assure a patient environment free of electrical shock and burn hazard to patients and staff; to assure Clinical Center compliance with standards of the Joint Commission on Hospital Accreditation; to take an active role in the formulation of national electrical safety standards; to participate in the activities of the Clinical Center Safety Committee; to inspect all new and renovated patient areas for proper grounding and electrical service, and to investigate electrical shocks and burns and issue written reports.

Major Findings: National standards which were not cost effective have been amended or eliminated with no increase in hazard to patients, CC patients' electrical environment has been made nearly accident free, hazardous electrical service to patient areas has been corrected, Clinical Center operating rooms have been changed to use nonflammable anesthetizing agents and we have advocated the use of non-conductive flooring in newly constructed operating rooms.

Significance: Clinical Center passed Joint Commission on Hospital Accreditation inspections with no electrical safety deficiencies, the number of incidents of reported electrical shocks and burns has been reduced, a cost and manpower saving has been realized by the switch to nonflammable anesthetizing agents and a similar saving will be made if our recommendation for non-conductive flooring for future construction is adopted.

Proposed Course: To investigate the feasibility of contracting parts of clinical and non-clinical equipment testing. Continue to revise national and local electrical safety standards to reflect increased awareness of electrical safety and regulatory activities of FDA toward manufacturers of medical devices.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10015-04 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheter for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J.L. Doppman	Chief	DR CC
	R. Jones	Engineering Technician	BEIB DRS

COOPERATING UNITS (if any)

DR-CC, MES-BEIB

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature toposcopic catheter attached to the end of a 1-mm #6 French catheter has been developed for insertion in tortuous blood vessels as small as 1 mm in diameter and up to 30 cm long. Catheter tests in anesthetized dogs have been highly successful - the catheter is able to penetrate parts of the vascular system which are unaccessible by existing techniques. The apparatus is being redisigned to provide the reliability and convenience required for clinical use. The catheter will enable the delivery of embolizing agents or other therapeutic substances so that some procedures previously requiring surgery can be performed instead with cathers. Techniques of steering the catheter are being developed.

ZO1 RS 10015-04 BEI

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels and steering it into selected branches.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel for clinical usage.

Major Findings: A miniature topographic catheter capable of negotiating tortuous paths has been successfully tested in dogs and will soon be ready for clinical use.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms, and other lesions with minimal danger to normal tissues. Delivery of embolizing agents and materials to stain tissue, as well as aspiration of fluid, are contemplated.

Proposed Course: Complete construction and testing of the clinical apparatus and then use the system clinically. Develop steering techniques, test in animals, and incorporate into the existing system. Develop related devices and explore additional uses for the catheter.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10018-04 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: P.M. Bungay Chemical Engineer BEIB DRS

COOPERATING UNITS (if any)

Department of Mathematics, University College, London

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptomatic solutions to the hydrodynamic equations, and the method of moments is employed to analyze the solute continuity equation.

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes, including such observations as "hindered diffusion".

Methods Employed: The essence of the approach is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogenous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigic pore wall, in general, increases the hydrodynamic resistance to translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. Where there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are regular and singular perturbation techniques (typically using the ratio of solute to poer dimensions as the asymptotic expansion parameter) and collocation techniques of the type developed by Weinbau, and Pfeffer.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for deriving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: Progress has been made in modeling the transport of neutral spherical solutes through long slit-like pores with plane parallel boundaries. Electron micrograph evidence suggest that slit-like geometry is typical of the junctions between endothelial cells. The dispersion analysis developed in the previous reporting period has been refined by incorporating numerical evaluation of the Ho and Leal integral expressions for the resistance coefficients of the first order in the ratio of sphere radius to slit width.

For neutral spherical solutes in cylindrical pores, derivation and evaluation have been completed for correction to the resistance coefficients of the second order in the spere-to-tube radius ratio. These results should lead to an improvement of the dispersion analysis of Gaidos and Brenner for convective and diffusive transport. In the present year the expressions were derived for the corresponding terms describing the additional pressure drop resulting from the presence of the sphere.

Also completed was the analysis for the asymptotic prediction of pressure drop versus flow in a cylindrical vessel with a constricted or dilated region.

Proposed Course: In addition to the models presently under study, it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle partical orientation and rotational Brownian motion effects. An ellipsoidal solute would be the likely choice in terms of posing theoretically tractable problems. Another direction to pursue, which would greatly extend the range of applications for the theory, would be to incorporate into the present models nonhydrodynamic solute-membrane interactions such as electrostatic or London Van der Walls attractive/repulsive forces.

Significance: Channels (pores, slitlike gap junctions) represent one important type of transmembrane transport in biological systems. A rigorous conceptual and predictive framework for pore theory would be useful in clarifying relevant biological transport and would find wide applicability in engineering and physical science work pertaining to synthetic membranes.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10019-04 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Instrumentation for Flow-Through Hollow Fiber Cell Culture Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	R.A. Knazek	Senior Investigator	LPP DCBD

COOPERATING UNITS (if any)

Laboratory of Pathophysiology - DCBD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As part of studies aimed at improving the methodology for hollow fiber cell culture and investigating the response of cultured cells to pharmacologic agents, instrumentation systems are being developed for measuring relevant culture parameters. Instrumentation has been designed and built for monitoring the rate of oxygen consumption using a Clark-type amperometric oxygen electrode. Work on an electrode for monitoring the extracellular oxygen partial pressure is continuing. subsequent parameters to be investigated are pH and carbon dioxide partial pressure.

Objectives: The short-range objective is to devlop sensor and instrumentation packages for monitoring cell metabolism and growth parameters of cells being cultured in hollow fiber units. The long-range objectives are to (1) elucidate factors beneficial to maintaining and promoting growth and (2) determine the response of cells to pharmacologic agents.

Methods Employed: In the hollow fiber cell culture units employed in this study, the hollow fibers serve as semipermeable membrane barriers between the cultures outside the fibers and nutrient solution perfused through the fiber lumen. The fibers (typically 200 m ID and 250 m OD) permit exchange of oxygen, carbon dioxide, nutrients, products of metabolism, and other chemical substances ranging in size up to that of proteins like albumin. The fibers are packed roughly parallel and closely spaced such that diffusional distances typically do not exceed 100 m. The fiber lumens are continuous with an external closed loop containing a nutrient solution and a pump to maintain recirculation of the solution through the pores. In some units two duplicate loops (hollow fiber bundle/reservoir/pump) are used; however, the two fiber bundles are braided together inside a single culture unit. The more complex systems are designed for studying convective as well as diffusive transport in the extracapillary space.

The effort thus far has been to develop the capability to measure (1) the rate of oxygen consumed by the cells in the unit and (2) the extracellular oxygen tension in the culture. Under steady conditions, the amount of oxygen given up by the nutrient solution in passing through the fibers is a measure of the rate of consumption by the cells. The connective tubing leading to the unit is of sufficient length so that the nutrient solution at the inlet to the culture unit is essentially saturated with respect to the carbon dioxide-enriched atmosphere. Measuring the difference in the partial pressure of the nutrient solution between the inlet and outlet of the culture unit permits calculation of the rate of delivery of oxygen to the cells using the medium flow rate and oxygen solubility. For this purpose an instrumentation package incorporating a Clark-type amperometric oxygen electrode has been assembled.

An electrode scheme for measuring the extracellular oxygen tension has been under development. The plan is to privide access for a fine wire electrode to the interior of a single nonporous, gas-permeable fiber in the bundle. The fiber will extend beyond both ends of the bundle and through the walls of the distribution caps covering the ends of the shell. Thus, the fiber will be bathed externally by the nutrient solution inside the caps, but will be exposed to the cell culture inside the shell. The fiber interior will be otherwise isolated and can be filled with a buffer solution appropriate to an electrode pair, such as platinum and silver/silver chloride. Current efforts are directed toward the fabrication of a long, slender, cylindrical probe incorporating the platinum electrode (exposed at the probe tip) and the silver/silver chloride electrode plated on the exterior cylindrical surface.

Proposed Course: After satisfactory development of the oxygen monitoring systems, techniques will be examined for measuring other important cell culture parameters. Among the parameters to be looked at next are pH and carbon dioxide partial pressure in the extracellular fluid.

NATIONAL SCIENCE INFORMATION SYSTEM
PROJECT NUMBER (Do NOT use this space)

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10022-03 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/pH Probe

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
	R.M. Winslow	Senior Investigator	H IR MH
	R.V. Fitzgerald	Physical Science Technician	BEIB DRS

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering and Mechanical Engineering Sections

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.7	0.3

CHECK APPROPRIATE BOX(ES)

[ ] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [X] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In the initial year of the project, a miniature pH sensor, based on fiber optics, was designed to pass through a 22-gauge needle intended for implantation in tissue for physiological studies during exercise. The operation of the probe depends on pH changes identified by dye indicators. The probe is connected to laboratory optical instrumentation.

During the second year, an electro-optic measuring and readout system was designed and developed specifically for the pH sensors. The new unit makes the overall system portable, practical, and easy to use. In vitro tests were performed to characterize the pH sensor and the instrument. In the current year, improvements in the probe were made, and its applicability to blood pH determination was shown.

Z01 RS 10022-03 BEI

Objectives: Develop a pH sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Enployed: A fiber optic measurement of dye indicator response to pH.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurements of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure). Alternately, measurements of the blood oxygen concentration can be used to determine oxygen pressure by this curve. Since the relation between oxygen pressure and concentration is affected by changes in pH which occur during exercise (shift in the curve with pH, the Bohr effect), it is necessary to incorporate a pH measurement with the oxygen measurement in making use of the curve.

Major Findings and Proposed Course: During the current year, improvements were made in the construction of the pH probe and the method of preparation of the pH sensitive packing, to give improved performance and stability. Although the pH probe was initially intended for use in tissue, it became of interest to evaluate its suitability for use in blood. In vitro blood tests and experiments in animals were done to evaluate the performance of the pH probe in blood. These tests demonstrated its applicability to blood pH measurement.

NIH-ADAMHA SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10023-03 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Two-Dimensional Ultrasonic Imaging System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	W.S. Friauf	Chief	EEES BEIB DRS
	T.E. Hall	Electronic Engineer	BEIB DRS
	J.L. Doppman	Chief	DR CC
	T.H. Shawker	Clinical Associate	DR CC
	W.C. Whitehouse	Electronic Technician	ADM CC

COOPERATING UNITS (if any)

DR-CC; ADM-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER X

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several subsystems of a comprehensive, versatile, ultrasonic imaging and recording system have been developed. A second-generation real-time mechanical sector scanner has been put into use along with a video system for consolidation, displaying, and recording a variety of data. The development of a solid-state sector-to-TV scan converter is completed. Work is continuing on a Doppler velocity measuring system designed to work in conjunction with the sector scanner. The overall system has proved to be especially useful in abdominal scanning and early detection of pregnancy.

Objectives: Development of a high-performance two-dimension real-time ultrasonic imaging system with provision for Doppler velocity measurements at a selected point and standard TV output to facilitate video tape recording of an examination, including the sector, a view of the patient, real-time clock, additional alpha numeric information, moving trace ECG and pressure data, voice commentary, and audio and/or visual presentation of velocity data. Additional objectives are versatility, that is, suitability for ocular, cardiac, pediatric, and abdominal scanning with minor changes, and high benefit/cost ratio.

Rationale: To be suitable for cardiac usage, among others, a sector scan is virtually essential. While a phased array system is elegant, comparable results can be obtained by mechanically oscillating a single transducer through the desired scn angle. The latter approach has the following advantages: (a) the cost is much lower; (b) no degradation of beam pattern occurs near edges of scan; (c) the single ultrasonic element can easily be changed to provide a resonance frequency which is optimum for the problem at hand and (d) with only one transducer element, much more sophisticated duplexing, amplification, and signal detection can be achieved at reasonable cost.

Methods Employed: Based on the positive results obtained with the mechanical scanner designed and built earlier, a second-generation mechanical sector scanner was developed. The size of the scanner and mechanical vibration have been substantially reduced. In addition, the new scanner maintains electrical control of the scan pattern through the use of position feedback, which provides three major advantages relative to earlier mechanical scanners: (a) lines are spaced uniformly throughout the sector; (b) synchronization with standard TV systems is easy--a feature which facilitates high-quality imaging in video format; and (c) the instrument can be programmed to execute one or two scans per second, each requiring 1/15 second, with the scanner stopped at the center of the scan the remainder of the time to allow Doppler velocity measurements guided by the position information. Stopping the scanner most of the time will be necessary in order to get a useful signal-to-noise ratio for the Doppler signal.

Major effort was directed to the development of a new device for converting the sector scan to video format. Digital storage in solid-state memory was developed with conversion to and from analog voltages at the output and input, respectively. Compared to present television camera scan converters, the solid-state unit provides a flicker-free display, thus facilitating concurrent spatial and velocity measurements as discussed above. Further, discrete scan lines are not imaged, and other image-processing or image-enhancing procedures can be readily incorporated. Reliability and ease of use has been greatly enhanced.

For the purpose of building up a TV picture with many types of information simultaneously for recording via video tape, appropriate commercial components have been assembled into a system.

Significance: The main significance is that, through suitable choice of approach, high-quality noninvasive visualization and recording can be achieved at a very reasonable cost.

Proposed Course: With the completion of the solid-state scan converter, a major effort will be made to improve image quality by adopting sophisticated techniques from other fields, such as radar and nuclear magnetic resonance, to the problem

of using the same transducer for transmission and reception. Concurrently, attempts will be made to incorporate range-gated pulsed Doppler velocity measurement capability at a reasonable cost. Techniques that may eleminate the need for costly high-frequency power amplifiers and spectrum analyzers are also being explored.

Publications:

Schuette, W.H., Shawker, T.H., and Hall, T.E.: Evaluation of a quarter wavelength matching layer transducer in abdominal scanning. J. Clin. Ultrasound 7: 65-66, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10027-03 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Development of Whole-Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	J. Whang Peng	Senior Investigator	MS DCT NCI
	R. Corsey	Electronic Engineer	BEIB DRS
	H. Tipton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

MC-DCT-NCI; CC-NIH; MS-DCT-NIH

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes development of an instrumentation and control ssytem based on utilization of a Tektronix 31 programmable calculator, digital plotter, and interface for data acquisition. The esophageal temperature of the patient is regulated to 0.1°C accuracy by feedback control of the temperature of water circulating in a set of hyperthermia blankets.

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record, and process data as well as to control water temperature of a set of hyperthermia blankets. The temperature of the water pumped through the blankets together with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to the flow stream returning from the blankets as directed by the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole-body core temperature of patients to 42.0 $\pm$0.1^{o}C for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for cancer is practical. Currently, the system is being employed in conjunction with chemotherapy.

Publications:

Lees, D.E., Bull, J., Whang-Peng, J., Atkinson, R., Schuette, W., and Macnamara, T.: Auscultatory Confirmation of Esophageal Temperature Probe Placement. In Proceedings of the American Society of Anesthesiologist Annual Meeting, Chicago, IL, Oct. 1978, pp. 551-552.

Lees, D.E., Bull, J., Whang-Peng, J., Schuette, W., W. Bynum, G., and Macnamara, T.: Innovar Modification of the Ventilatory Response to Extreme Hyperthermia in Man. In Proceedings of the American Society of Anesthesiologist Annual Meeting, Chicago, IL, Oct. 1978, pp. 615-616.

Kim, Y.D., Lees, D.E., Bull, J., Whang-Peng, J., Schuette, W., and Macnamara, T.: Hyperthermic Potentiation of the Alpha-Adrenergic Blockade Induced by Droperidol. In Proceedings of the American Society of Anesthesiologists Annual Meeting, Chicago, IL, Oct. 1978, pp. 631-632.

Kim, Y.D., Lees, D.E., Bull, J., Whang-Peng, J., Macnamara, T., and Schuette, W.: Hemodynamic and Blood Gas Changes with Whole Body Hyperthermia. In Proceedings of the American Society of Anesthesiologists Annual Meeting, Chicago, IL, Oct. 1978, pp. 331-332.

Schuette, W.H., Bull, J.M., Lees, D.E., Whang-Peng, J., Atkinson, E.R., and Smith R.: Time-Temperature Normalization During Hyperthermia Treatment. In Proceedings of the 31st Annual Conference on Engineering in Medicine and Biology 20: 294, 1978.

Bynum, G.D., Pandolf, K.B., Schuette, W.H., Goldman, R.F., Lees, D.E., Whang-Peng, J., Atkinson, E.R., and Bull, J.M.: Induced Hyperthermia in Sedated Humans and the Concept of Critical Thermal Maximum. American Journal of Physiology: 4/3, Nov. 1978, R228-R236.

Schuette, W.H., Lees, D.E., Bull, J.M., Tipton, H., Kim, Young Duk, Whang-Peng, J., Smith, R., and Bynum, G.D.: Feedback Control of Esophageal Temperature During Whole Body Hyperthermia. Advances in Bioengineering, American Society of Mechanical Engineers, New York, 1979, pp. 109-110.

Lees, D.E., Schuette, W., Bull, J., Whang-Peng, J., Atkinson, R., and Macnamara, T.: An Evaluation of Liquid-Crystal Thermometry as a Screening Device for Intraoperative Hyperthermia. Anesthesia and Analgesia, Vol. 57, No. 6, Nov. 1978, pp. 669-674.

Lees, D.E., Kim, Y.D., Schuette, W.H., Bull, J.M., and Whang-Peng, J.: Causes of Induced Hyperthermia. Anesthesiology 50: 69-70, 1979.

Bull, J.M., Lees, D.E., Schuette, W.H., Whang-Peng, J., Smith, R., Bynum, G., Atkinson, R.E., Gottdiener, J.S., Gralnick, H.R., Shawker, T.H., and DeVita, V.T.: Whole body hyperthermia-A PHASE I trial of a potential adjuvant to chemotherapy. Annals of Internal Medicine 90: 317-323, 1979.

Owens, S.W., Lees, D.E., Schuette, W.H., Thibault, L.E., Bull, J.M., and Whang-Peng, J.: The Effect of Thermally-Induced Respiratory Alkalosis on Erythrocyte 2,3DPG Levels and Hemoglobin P_{50} Determinations. In Proceedings of 53rd Congress International Anesthesia Research Society, March 11-15, 1979, Hollywood, Florida.

PROJECT NUMBER (DO NOT use this space)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10029-02 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Modulation of Transendothelial Mass Transport By Hydrodynamically Induced Steady and Unsteady Wall Shear Stress.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechnical Engineer	ACES BEI3 DRS
OTHER:	R. Dedrick	Chief	ChES BEIB DRS
	D. Fry	Chief	IR EA NHLBI
	W. Schuette	Chief	ACES BEIB DRS

COOPERATING UNITS (if any)

IR-EA-NHL_I

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	.75	.75

CHECK APPROPRIATE BOX(ES)

[ ] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [X] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analytical and experimental investigations have been completed which define the flow field in an apparatus designed to apply a controlled shear stress field to the endothelial surface of canine aorta in vitro. Permeability studies using Evans Blue Dye labelled albumin are in progress. Steady shear fields have been applied to the endothelial surface and changes in uptake of the tracer protein molecule are being measured. Mechanical properties of the aorta wall are also being determined.

Objectives: It is believed that mechanical factors play a role in the atherosclerotic process. Local hemodynamic events produce forces which cause the aortic wall to be stressed. This study has been undertaken in an attempt to isolate one of those stresses, namely the hydrodynamically induced wall shear stress. Simultaneously, changes in permeability of the aortic wall in response to stress are studied using tracer protein molecules.

Methods Employed: An analytical solution for the shear field in a fluid rotating in a region at the ends of concentric finite cylinders has been obtained. The electrochemical technique for the measurement of shear stress, dye injection studies and dynamic pressure measurements have been performed to validate the analysis.

Major Findings: Thus far, permeability of the endothelial surface to albumin appears to be only weakly dependent on steady shear stress to levels of 100 dynes/cm^2 with a much stronger dependence above that level. Unsteady sheer stress (both temporal and spatial) appears to alter permeability much more dramatically.

Significance: In order to study the influence of a variety of mechanical factors and their role in the atherosclerotic process, factors must be studied in isolation. Our methods isolate for study the steady and unsteady wall shear stress effects on the modulation of endothelial permeability.

Proposed Course: To investigate the unsteady shear stress in more detail. To develop video techniqies for processing the uptake data.

PROJECT NUMBER (DO NOT USE THIS SPACE)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10033-02 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Micropipette Pressure Transducer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	D.L. Fry	Physiologist	NHLBI.

COOPERATING UNITS (if any)

NHLBI

LAB./BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.3	0.3

CHECK APPROPRIATE BOX(ES)

[ ] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [X] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A pressure transducer with a micropipette tip, 10 in diameter, and infinite direct current input impedance, is being developed.

Objectives: To be able to measure pressure gradients within arterial walls, or within other spaces where a tiny probe of infinite static fluid stiffness is required.

Methods Employed: A servo-balance design, utilizing a primary and secondary transducer and a piezoelectric actuator for balancing, is being employed. Accurate temperature control will also be maintained.

Major Findings: The first stage of the device has been constructed, and preliminary tests show the concept to be feasible.

Significance: This device should be useful for research in atherosclerosis and other studies in which intra- or intercellular fluid pressure is an important factor.

Proposed Course: After final construction, the system will be thoroughly tested in vitro.

MATHEMATICAL SCIENCE INFORMATION - NUMBER PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10034-02 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Three-Dimensional Histological Reconstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: S.B. Leighton Mechanical Engineer BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

[ ] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [X] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A semi-automatic system for acquisition of three-dimensional structural information about histological material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a scanning electron microscope imaging system, the surface of the block will be imaged and stored, and successive slices will be removed by a built-in microtome. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction.

Objectives: (1) To facilitate making schematic diagrams of neural nets. (2) To facilitate developmental studies of small organs and organisms.

Methods Employed: Various cutting, staining, and imaging techniques are being evaluated for best resolution.

Major Findings: So far, the feasibility of the project has been demonstrated, and resolutions to 600 Angstroms have been achieved in neural tissue. Preliminary design of the miniature microtome is complete.

Significance: Neoroanatomists may be able to trace significant neural nets easily enough to do enough samples to be statistically significant.

Proposed Course: A complete device will be constructed and integrated with an S.E.M.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10035-02 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Counter-Current Chromatography Without Rotating Seals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	I. Ito	Visiting Scientist	LTD NHLBI

COOPERATING UNITS (if any)

LTD-NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.1	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An improved mechanical design has been developed for a rotating counter-current chromatographic system without rotating seals. The design permits reliable operation in centrifugal fields up to 165 g, with independent control of spiral column rotation with respect to the field.

Z01 RS 10035-02 BEI

Objectives: To permit reliable, effective liquid-liquid current-current separations without any rotating fluid seals.

Methods Employed: A double, epicyclic gear train is used to permit independently controlled speeds, a compact, stable structure, and topology within the constraints of the no rotating seals concept.

Major Findings: The instrument is essentially complete.

Significance: The device will allow the laboratory of technical development, NHLBI, to pursue further studies in liquid-liquid chromatography.

Proposed Course: The instrument will be delivered to NHLBI for further testing.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10036-02 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Endoscope Introduction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	L. Bernstein	Internal Medicine	NLM

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A new technique for the introduction of endoscopes or catheters has been developed further. It makes use of the everting tube concept patented by Zeimar in 1970. It has been shown that it is feasible to keep the leading edge of an endoscope at the loading edge of an everting tube, and a patent application has been filed for this concept. Further development is delayed pending additional funding.

Objectives: To facilitate endoscopic examination and operation.

Methods Employed: New materials (urethane) and lubricants are being used to extend the concept of the original patent and permit practical application.

Major Findings: Urethane is a practical material for the proposed instrument, but wall thickness and durometer value must be closely controlled. Precise mechanical design will be required.

Significance: The difficulty of introducing endoscopic instruments is a significant impediment to their greater use. If this device can reduce that difficulty, the applicability of endoscopic examinations may be extended.

Proposed Course: Contingent on funding, further prototypes will be designed and tested, scaling up to a full-size, clinically useful instrument.

INTRAMURAL SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10038-02 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Zeugmatography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.I. Hoult	Electronic Engineer	BEIB DRS
OTHER:	J.W. Hansen	Neonatologist	NPMB NICHD
	S.R. Goldstein	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.4	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A nuclear magnetic resonance (NMR) imaging system is proposed for diagnostic studies, especially in babies. Zeugmatography provides an image of fluid collections and, therefore, could be useful in the diagnosis of conditions such as hydrocephalus, cystic malformations, intercranial bleeding, kidney malfunction, and congenital heart disease. A feasibility study has been completed, and the design of a suitable magnet and NMR spectrometer is now in progress. The magnet will employ windings on two hemispherical shells and consume about 10 kw of power. The spectrometer will operate at about 5 MHz and will employ a receiving coil and preamplifier with negative feedback in order to reduce the receiver dead time while not degrading sensitivity. The imaging method to be employed will depend on the experiment, but will normally be the rotating frame zeugmatography method developed in this laboratory.

Z01 RS 10038-02 BEI

Objectives: Explore the medical applications of zeugmatography, which is an imaging system that utilizes nuclear magnetic resonance (NMR) to detect fluid collections. Develop a zeugmatographic instrument to detect fluid-filled lesions in babies and limbs of adults.

Methods Employed: The technical difficulties involved in scaling zeugmatography experiments from normal NMR sample size (5 mm) to adult human dimensions (40 cm) are immense. Several laboratories are undertaking such a task in view of the possibility rich gains in the fields of cancer, cardiac, and metabolic research. Briefly, the problems involved in such scaling are lack of sensitivity (and thus resolution), excessive magnet power consumption, and receiver dead time following the pulse of radio frequency power required to stimulate the nuclei. If, however, the subject is a baby, the rewards, in terms of diagnosis of fluid-related conditions, are also rich, but the technical problems are less severe.

A feasibility study has been made of a magnet design and a new method of obtaining images. The study has indicated that the method may be applied with the consumption of modest amounts of power to obtain images with a resolution of the order of 1 mm in a 10-cm sample. The building of a novel magnet comprising two hemispherical shells is well underway. The problem of a receiver dead time has been solved, to a large extent, with the aid of negative feedback which dampens the ringing of the signal-receiving coil without introducing extra noise. The construction of a suitable spectrometer is almost complete.

Significance: Possible applications of small imaging system include the detection of fluid-filled cysts or dilations in the brain (hydrocephalus, cystic malformations, intercranial bleeding, etc.) abscesses, other fluid-filled cysts (kidney), and abnormal vasculature (congenital heart disease, atrioventricular malformations, etc.). Further, the instrument would be sufficiently large to accommodate adult extremities and thereby find use in the diagnosis of, for example, various arthritic conditions.

Proposed Course: Finish construction of an NMR spectrometer suitable for imaging, fluid-filled lesions in babies. Evaluate the instrument, using animals as subjects.

Publications:

Hoult, D.I., Fast recovery, high sensitivity NMR probe and preamplifier for low frequencies. Rev. Sci. Instrum. 50: 193, 1979.

Hoult, D.I., Rotating Fram Zeugmatography. J. Magn. Res. (In press).

Hoult, D.I., Rotating Frame Zeugmatography. Phil. Trans. Roy. Soc. (London). (In press).

Hoult, D.I., The Solution of the Bloch Equations in the Presence of a Varying B_1 Field. J. Magn. Res. (In press).

INTRAMURAL SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10039-02 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Biophysical Instrumentation and Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to develop new instrumentation and methodology or improve existing instrumentation and methodology for characterization of biological macromolecules. Analytical ultracentrifugation and techniques ancillary to it are the major areas of interest.

Objectives: To develop data acquisition systems for analytical ultracentrifuges and for ancillary equipment such as plate or film readers and densimeters and to develop appropriate software to use with the acquisition systems.

Methods Employed: A Digital Equipment Corporation PDP-8 computer has been acquired and is presently being interfaced with the ultracentrifuges and the ancillary equipment. Consideration is being given to the design factors involved in the development of a photon-counting fluorescence scanner for the ultracentrifuge.

Significance: The development of a suitable data acquisition system is expected to result in both qualitative and quantitative improvements in ultracentrifugal investigations. Data acquisition is presently the limiting factor in both of these aspects of such research. The development of a photon-counting fluorescence scanner is expected to increase the sensitivity of the ultracentrifuge by one to two orders of magnitude and should greatly facilitate the investigation of strongly interacting systems of macromolecules.

Proposed Course: Continue the developments outlined above.

INTRAMURAL SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10040-02 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Physical Chemistry of Biological Macromolecules

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	J.A. Gladner	Research Chemist	LCB NIAMDD
	S.I. Chung	Research Chemist	LB NIDR
	J.S. Finlayson	Director	PDB BB
	R. Shrager	Mathematician	LSMM DCRT
	A. Bhattacharjee	Research Chemist	LC NIAMDD
	L. Hjelmeland	Staff Fellow	DPB NICHHD
	T.J. Henry	Expert	LMB NCI
	B.J. Graham	Staff Fellow	LDNATV NCI

COOPERATING UNITS (if any)
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Uniformed Services University School of Medicine, Bethesda, MD 20014

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Biomedical Engineering and Instrumentation

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INSTITUTE AND LOCATION
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TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the physical properties of a wide variety of biological macromolecules with the goal of correlating these properties to the structure and function of the macromolecules. The emphasis is on molecular size and shape, the thermodynamics of molecular interactions, and on molecular weight distributions. Analytical ultracentrifugation is the principal research technique used.

Objectives: To study the structure of lamprey fibrinogen by means of determining the sizes of the native molecule and the constituent chains; to determine the molecular weight and study the possible aggregation properties of the D fragment of human fibrinogen; to determine the molecular weight and the partial specific volume of an acetylated lipopolysaccharide from E. Coli; to measure the critical micelle concentration, aggregation number, and equilibrium constant, and to calculate the changes of standard free energy, enthalpy and entropy for micele formation of deoxycholate derived zwitterion detergents; to measure the cesium chloride gradient bouyant densities of various nucleic acids; to study methods for the analysis of molecular weight distributions from ultracentrifugal data.

Methods Employed: The various macromolecules have been isolated and purified from appropriate sources by conventional means or have been prepared synthetically. The molecular weights have been determined by equilibrium ultracentrifugation and the resultant data has been analyzed by mathematical modeling techniques using the MLAB system on the DEC-10 computer. Mathematical modeling techniques have also been used for the studies on methods of analyzing molecular weight distributions.

Major Findings: Extensive studies on intact lamprey fibrinogen in normal and in denaturing solvents and on the isolated constuent chains in denaturing solvents completely support our earlier work which led to the postulation of one large alpha chain and two each of the beta and gamma chains representing the structure of lamprey fibrinogen. These studies also support the earlier observation of an anomolous value for the partial specific volume in denaturing solvents.

The studies on the D fragment of human fibrinogen are still in an early phase where we are building up a sufficient body of experimental data in order to not only determine the molecular weight, but also to determine the effect of the method of preparation and the effect of the solvent upon the state of aggregation.

The measurement of the molecular weight and partial specific volume of the acetylated lipopolysaccharide from E. Coli has presented unique problems. This material is soluble only in halogenated hydrocarbons. This has led to the use of dichloromethane, chlorobromomethane, and dibromomethane as solvent systems. By centrifuging the material in any two of these colvents at the same time, it is possible to solve for the partial specific volume as well as the molecular weight. However, the use of organic solvent systems provides the added complication of varying density as a function of radial position because of the solvent compressibility. This problem can be resolved experimentally, and the conclusion of this problem depends upon this and upon determining to what extent possible degradation of the lipopolysaccaride might have occurred.

The studies on the deoxycholate derived detergents is still in an early phase where a body of data is being accumulated and analyzed.

Cesium chloride gradient bouyant densitied have been measured for DNA from herpes simplex type I and type II viruses and from virus-like particles from mouse Leydig cells. These measurements were performed as services for Drs. Bartkoski, Graham, and Henry respectively.

The studies on obtaining molecular weight distributions from ultracentrifugal data has involved determination of the necessary criteria for obtaining these distributions using regularization techniques. In spite of the fact that this is a mathematically ill-conditioned problem, we have had quite good success in fitting both symmetrical and skewed unimodal distributions. The quality of fit obtainable for bimodal distributions has been less satisfactory, but is still at least as good as has been obtained by other methods. The quality of fit to trimodal and higher modal distributions has not been particularly satisfactory. The methods we are exploring appear to be quite promising in terms of effectiveness and efficiency in dealing with this problem, but the time required for programming makes progress slow.

Significance: The studies on lamprey fibrinogen and on the D-fragment of human fibrinogen are relevant to a basic understanding of the structure of the fibrinogens, to an understanding of their antigenicity and to an understanding of the action of plasmin on fibrinogen; these all relate to the role of fibrinogen in normal and pathological blood clotting. The studies on E. Coli cell surface lipopolysaccharide are relevant to the biological activity of the organism, both with respect to the function of the organism and with respect to its interaction with a host organism. The deoxycholate derived zwitterion detergents show considerable promise as non-denaturing detergents for the solubilization of membrane proteins. Knowledge of the physical properties of these detergents is desirable to correlate with the effectiveness of such detergents in solubilizing specific proteins. The bouyant density of a DNA is considered an important characterizing parameter since they tend to vary between normal and abnormal DNA's and between native and denatured DNA's. The bouyant densities reported here were performed as services for the concerned investigators (Drs. Bartkoski, Graham, and Henry). Success in dealing with the problem of measuring molecular weight distributions is of considerable importance if several significant studies are to be undertaken with any prospect of success. This has long been one of the major problems in ultracentrifugal analysis and a significant improvement in methodology here would be an important achievement.

Proposed Course: The studies on lamprey fibrinogen have been completed and a manuscript is in preparation. The work on the fibrinogen D-fragment, the lipopolysaccharide, the deoxycholate derived zwitterion detergents, and the molecular weight distributions will continue. Studies on radiation-induced cleavage of proteins and polypeptides, on rhodopsin, on receptor site molecular weights, and onprotein self-associations are planned.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10041-02 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Flow Visualization Studies and Hemodynamic Events in Model Arteries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
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	D.L. Fry	Chief	H IR OD

COOPERATING UNITS (if any)

OD - IR - NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.4	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to investigate the patterns of flow in models of arterial geometris and to seek correlations between these flow patterns and the development of atherosclerotic plaques. In previous studies, quantitative measurements of the wall shear stress were made in model arteries by an electrochemical technique. However, the work provided no information about the direction of the shearing forces, and little idea about the nature of the flow patterns. In this study we will use various methods of flow visualization such as dye injection, hydrogen bubbles, and neutrally buoyant microsphere tracers to study the flow patterns in arterial models as a function of various flow parameters such as Reynolds number, branch flow ratios, and pulsatility. Both still photography and high-speed cinematography will record the flow phenomena. The work is in preliminary development stages, and various flow visualization techniques are being evaluated and refined. The electrochemical technique will be used to measure average mass transfer coefficients to the artery wall under conditions of steady and pulsatile flow.

Objectives: The objectives of this study are to visualize and record the various kinds of flow phenomena such as flow separation and secondary flow that may occur in complex flow channels that represent arterial geometry and to correlate the flow phenomena with the location of atherosclerotic plaques in experimental animals. The analysis will include a quantitative measure of the velocity profiles at various sites in the model arteries. In conjunction with these experiments, measurements will be made of the mass transfer coefficients to the walls of the model arteries under conditions of both steady and pulsatile flow.

Methods Employed: Several methods have already been shown to be useful for visualizing flow patterns in our model systems, and other methods will be tried. The electrochemical method of measuring mass transfer coefficients will be used in several model systems. In the preliminary phases of this work, the following techniques have been used.

(1) Dye injection. At selected sites in the arterial model, small ports are drilled for insertion of #30 gauze hypodermic tubing, which is connected via PE 10 catheter tubing to a reservoir of colored dye. The end of the hypodermic tubing can be positioned at any radial location in the flow model and the dye slowly injected into the flow to mark the streamlines. The streamline patterns at several sites can then be recorded using 35-mm still photography. Initial data obtained by dye injection into the flow indicates that the flow streamlines are skewed toward the side-arm branches exiting from the main (aortic) flow channel and that unusual patterns of backflow and secondary flow occur near the channel wall just opposite the branch orifices.

(2) Hydrogen bubble technique. At selected sites in the arterial model, small grooves are milled into the model for the installation of 3-mil stainless steel wire. Several wires run across the diameter of the flow channel at locations in both the main branch and the side branches. The wires serve as cathodes in a system consisting of a remote anode and an electrolytic solution of sodium chloride. By pulsing a DC current through the system, hydrogen bubbles are evolved all along the cathode wire, which are in turn swept away by the flow. In such a manner, each element of fluid passing the wire is marked by the visible hydrogen bubbles and the shape of the velocity profiles can be recorded with appropriate photography.

(3) Neutrally buoyant microspheres. This method employs a dilute suspension of 100- to 500-micron diameter polystyrene microspheres in a 20 to 25 percent glycerine/water solution, which serves as the test fluid in the flow model. The microspheres are dyed with a fluorescent dye and then illuminated with ultraviolet light making them clearly visible in the flow system. The path of the microspheres can be photographed with high-speed cinematography as these neutrally buoyant particles move along with the fluid. In such a manner, the direction and velocity of fluid elements can be determined.

(4) Laser Doppler velocimetry. When light is scattered from a moving object, a stationary observer will see a change in the frequency of the scattered light (Doppler shift) proportional to the velocity of the object. This Doppler shift is used to measure the velocity of particles at various locations in the fluid. From the particle velocity, the fluid velocity is inferred. A laser is used as the light source because it is easily focused and coherent. This method allows us to determine, quantitatively, the velocity profiles at various positions in the arterial model.

Significance: Elucidation of the role of hemodynamics on the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease. Certain biological evidence suggest that areas of increased plaque formation may correlate with areas frequently exposed to disturbed flow, for example, flow separation, or to relatively stable flow patterns that change direction and magnitude periodically throughout the day with varying metabolic and blood flow demands. This study should demonstrate various types of flow patterns that can occur in arterial systems as a function of changing flow parameters. Likewise, the mass transfer of blood borne constituents like oxygen or lipoproteins can be affected by the flow patterns in various regions near the artery wall. An imbalance in the mass transfer of these elements can cause either vascular damage or excess accumulation of lipids which can eventually lead to a pathological state in the artery wall.

Proposed Course: (1) Design and fabricate arterial models. (2) Study the flow patterns in these models using the various techniques described above as a function of several flow parameters such as Reynolds number, branch flow ratio, and flow pulse frequency. (3) Correlate these findings with those of our previous experiments on wall shear stress in similar models. (4) Determine the mass transfer coefficients to the arterial wall as a function of various Schmidt numbers under conditions of steady and pulsatile flow. (5) Correlate all hemodynamic evidence with incidence of lesions in experimental animals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10042-02 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

The Use of Microprocessor-Based "Intelligent" Machines in Patient Care

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Eden	Chief	BEIB DRS
OTHER:	H. Eden	Assistant to the Chief	BEIB DRS
	P. Bungay	Chemical Engineer	BEIB DRS
	W. Friauf	Chief	EEES BEIB DRS
	B. McLees	Chief	DCCM CC
	K. Kempner	Electronics Engineer	CSL DCRT
	R. Martino	Electronics Engineer	CSL DCRT
	R. Branson	Georgetown University	
	N. DeClaris	University of Maryland	
	T. Field	Franklin Pierce Law Center	
	M. Frankel	Wayne State University	
	C. Spiegel	George Washington University	
	A. Teich	Technoscience Associates	
	K. Warner	University of Michigan	

COOPERATING UNITS (if any)

Georgetown University; University of Marvland; Franklin Pierce Law Center; Wayne State University; George Washington University; Technoscience Associates; University of Michigan

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As part of NIH's overall Consensus Development effort, BEIB is planning to host a conference on "The Use of Microprocessor-Based 'Intelligent' Machines in Patient Care" on October 17-19 in the Washington, D.C. area. The branch will provide conference participants with a set of introductory working papers which arose out of four planning workshops in 1978. The participants to the upcoming conference will seek agreement on social and technical issues underlying the development of medical systems which contain microprocessors.

ZO1 RS 10042-02 BEI

Objectives: To identify, clarify, and preliminarily assess the technical and social issues underlying the development of microprocessor-based "intelligent" machines for patient care--especially as they relate to systems capable of autonomously adjusting treatment of patients.

Methods Employed: NIH and non-NIH members of the academic community are meeting in an open conference in an attempt to reach a consensus on (1) the technology's current state-of-the-art, (2) its prospects for future development, and (3) a preliminary view of its potential, long-range, legal, ethical, social, medical, and economic implications.

Significance: The traditional, passive role that machines have played in the delivery of health care is being radically altered by recent developments in data processing, pattern recognition, and electronics microcircuitry. Machines capable of emulating intelligent behavior and making "judgments", independent of continuous physician supervision, may soon be developed for patient care; this study addresses the technological and social issues that such prospects raise.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10043-02 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/Oxygen Probes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
	R.M. Winslow	Senior Investigator	H IR MH

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Successful development of a fiber optic pH probe has provided a model for the extension of this approach to the construction of other probes, the most important being an oxygen probe. Effort during the previous year had been devoted to attempting to develop a suitable color absorption indicator for oxygen, a continuation of this effort led to the conclusion that this was too difficult a problem to solve, so the work was redirected toward evaluating the feasibility of using the principle of oxygen quenching of fluorescence.

ZO1 RS 10043-02 BEI

Objectives: Develop an oxygen sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Employed: A fiber optic measurement of dye-indicator response to oxygen.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurements of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure).

Major Findings and Proposed Course: The key ingredient for construction of a fiber optic oxygen sensor is some color sensitive indicator for oxygen. Efforts to develop a light absorption indicator (since none is available) were unsuccessful, and continued effort in this direction would require more expenditure than seems justified. Use of the principle of oxygen quenching of dye fluorescence was an alternative, and experiments have shown that appropriate materials and dyes can be obtained which are compatible with the use of plastic optical fibers. Work is continuing on development of a probe using this principle.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10050-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Positron Emission Tomography Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. DiChiro	Section Chief	SN NINCDS
OTHER:	R.A. Brooks	Senior Staff Fellow	SN NINCDS
	V.J. Sank	Research Physicist	SN NINCDS
	W.S. Friauf	Electrical Engineer	BEIB DRS
	S.L. Leighton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

SN NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
EEES, MES

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A custom PET scanner is being developed to provide compromises between resolution, sensitivity, count rate capability, and cost that are optimal for human neurological research requirements at NIH.

PHS-6040
(Rev. 10-76)

Objectives: Design and have built a PET scanner with higher resolution than other custom or commercial machines, but without excessive compromise of sensitivity or count rate capability.

Methods Employed: The design will feature a large number of BGO detectors more tightly packed in a smaller ring than other designs, with electronic advances to shorten the coincidence window to a minimum, thus easing the random coincidence problem which is aggravated by a small ring. A novel detector motion has been developed to further improve resolution.

Major Findings: Analysis of the proposed design and experimental work with BGO detectors both suggest that a considerable advance in PET scanning is feasible.

Significance: PET imaging with a variety of positron emitting tracers allows many metabolic processes to be studied spatially. The new scanner will increase the spatial resolution which currently limits the potential of the approach.

Publications:

Brooks, R.A., Sank, V.J., Talbert, A.J., and DiChiro, G. Sampling Requirements and Detector Motion for Positron Emission Tomography. IEEE Transactions on Nuclear Science, Vol. NS-26 (In Press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10051-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Monolithic Thermopile

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.S. Friauf	Electrical Engineer	EEES BEIB DRS
OTHER:	C. Mudd	Mechanical Engineer	MES BEIB DRS
	R. Berger	Section Chief	LTD NHLBI

COOPERATING UNITS (if any)

NBS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1	1	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Process technology developed by the semiconductor industry should be ideal for thermopile fabrication, allowing improvements which will be reflected in advanced state of the art of micro-calorimetry, with many applications to biochemical research. A monolithic thermopile has been designed and will be fabricated in small quantities by NBS using conventional integrated circuit technology. Analysis indicates that an order of magnitude improvement in sensitivity relative to the present state of the art should be possible with the same sample volume, with the potential of maintaining this sensitivity for much smaller volumes.

Next steps include device fabrication and testing, adaptation of the calorimeter to the new device, and system evaluation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10052-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Laser Doppler Measurement of Tissue Blood Flow

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.F. Bonner	Physicist	BEIB DRS
OTHER:	T.Clem	Electrical Engineer	BEIB DRS
	P.D. Bowen	Biologist	LTD NHLBI
	R.L. Bowman	Chief	LTD NHLBI
	A. Tahmoush	Assistant Neurologist	NB NINCDS
	R. Nossal	Research Physicist	PSL DCRT

COOPERATING UNITS (if any)

BEIB, DRS; LTD, NHLBI; NB, NINCDS; PSL, DCRT

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	0.8	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A real-time tissue blood flow monitor has been developed based on the velocity-dependent Doppler broadening of laser-light scattered by moving red blood cells within living tissues. A physical theory has been developed which explains the observed Doppler broadening of laser-light diffusing through tissue and formed the basis of a new instrument design. This instrument has demonstrated linear dependence on flow in a variety of animal and human tissues. The instrument monitors pulsatile flow with cardiac cycle as well as mean flow and has been used to characterize transient changes in the microvasculature. A clinical investigation of muscle blood flow at biopsy is being pursued in order to correlate the state of the microvasculature with various muscular diseases. Further development of the theory and instrumentation will be directed toward extending the clinical and research use of the technique at a variety of tissue sites.

Objective: The objective of this project is to develop and test a clinical and research instrument, based on laser Doppler velocimetry, capable of measuring changes in local tissue blood flow. The project has three facets: (1) develop a physical theory of Doppler shifts from tissue, (2) develop a simple-to-use instrument with flexible fiber optic light path and electronic processor with linear response to a large range of flow states, and (3) evaluate clinical usefulness of the device.

Major Results: A physical model has been developed which accurately predicts the shape and half-width of the observed Doppler spectra from various human tissues. This model clarifies the information content in the detected signal and justifies a flow parameter based on the normalized first moment of the power spectra. The instrument development has included (1) that of a flexible fiber optic path capable of delivery and detection of the laser-light to and from the tissue to be studied, and (2) an electronic analogue processor to determine the normalized first moment of the power spectrum corrected for noise sources. This electronic processor gives a continuous output linearly-related to flow capable of resolving the fine structure of the pulsatile flow with cardiac cycle as well as slower changes in mean flow. Currently the ability of the instrument to measure a broad range of blood flow levels in a number of different tissues is being examined.

Proposed Course: A clinical protocol is being established to evaluate its usefulness as a monitor of resting blood flow, reactive hyperemia, and response of the microvasculature to external pressure, at a number of muscle sites immediately prior to biopsy. This protocol proposes to examine correlations between the state of the muscle microvasculature and various muscle diseases. After this trial, it is proposed to extend its clinical testing to the evaluation of skin graft viability and in the evaluation of peripheral circulatory problems. Research use in animals will also include evaluation of vasoactive pharmaceuticals. Future refinement of the physical theory and electronic processor will be directed toward extension of the device to tissues containing large superficial vessels and with the aim of broadening the applicability of the technique.

PUBLIC HEALTH SERVICE PROJECT NUMBER (DO NOT use this space)	DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 10053-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Membrane Based Sampling Systems for in In Vivo and In Vitro Kinetic Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	J.P. Froehlich	Senior Investigator	GRC NIA
	R.L. Berger	Section Chief	LTD NHLBI
	J. Fenstermacher	Section Chief	LCHPH DCT
	R.L. Dedrick	Section Chief	ChES BEIB DRS

COOPERATING UNITS (if any)

Gerontology Research Center-NIA; Laboratory of Technical Development-NHLBI; Laboratory of Chemical Pharmacology-DCT.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Synthetic membranes are being utilized in kinetics studies to provide a means for continuous sampling of the liquid from the system under study. In one application sampling equipment is being developed for in vitro study of calcium ion transport and calcium-ATPase activity in suspension of sarcoplasmic reticulum vesicles prepared from homogenates of rabbit muscle. In a second application a study of the mannalian blood brain barrier permeability is being aided by the development of an apparatus incorporating a sampler in an arteriovenous ex vivo shunt. In the latter plasmapheresis application pooling the plasma filtrate yields a single sample from which product of the plasma concentration and time integral can be evaluated for a chemical administered to the animal. Such sampling systems can be useful for the study of the kinetics of other fluid phase systems for which a membrane can be found which is permeable to one chemical of interest but impermeable to another necessary reagent or sink. Thus, other applications might be found in the areas of enzyme kinetics, pharmacokinetics, and the membrane transport of vesicle and cell suspensions.

Objectives: The principal objective is the development of the capability for fluid sampling based upon synthetic membrane technology. In many potential applications sampling by filtration or ultrafiltration may be more appropriate than alternative sampling technique. Ultrafiltration membranes allow the formation of samples representative of the free concentration of small soluble substances. These membranes will retain within the system under study macromolecules and those substances which are bound to them as well as colloidal or cellular components of the system. Other applications may call for the use of larger pore diameter membranes of, for example, macromolecules are to be sampled as well.

Methods Employed: The sampling system generally consists of three elements: (1) a module or modules containing sampling membranes, (2) sample collection equipment, and (3) a means for controlling the rate of production of sample. The membrane module is designed so that the membrane forms a part of the wall of the channel through which the liquid to be sampled flows. Only a small fraction of the liquid is diverted across the membrane to form the sample. The sample is produced as a consequence of a difference in pressure imposed across the membrane. The rate of production of the sample is regulated either by controlling the transmembrane pressure difference or through use of a sample metering pump.

Significance: Membrane sampling is being applied to studies of the transport of calcium ions across sarcoplasmic reticulum (SR). The transport studies are performed in vitro on a suspension of SR vesicles in buffer; the vesicles being created by homogenizing rabbit muscle. The kinetics of calcium uptake by or efflux from the vesicles can be followed by monitoring the appearance or disappearance of calcium from the suspending medium. Also, changes in levels of ATP and inorganic phosphate can be used to infer the kinetics of the calcium dependent membrane ATPase. The membrane in the sampler retains the vesicles (which are thought to be in the range of 0.1-0.5 m in diameter), so that the sample is representative of the suspending media.

A second application concerns in vivo studies of transport across the blood brain barrier. The initial objective is the determination of the barrier permeability to selected marker substances. In these experiments a sampler is connected in line with an extracorporeal arteriovenous shunt. By continuously and steadily drawing off a cfraction of the shunt flow through the sampler membrane, one can integrate over time the concentration of the marker substances present in the plasma. The value of the integral, together with a determination of the amount of the substance taken up by the brain over the same time interval, permits a determination of the permeability-area transport coefficient. A membrane which retains blood cells is of use in studies in which the transport of the substance into blood cells is sufficiently slow that the cells cannot be considered in equilibrium with the plasma. Use of ultrafiltration membranes may permit determination of the free concentration - time integral, rather than the integral for total plasma concentration, in circumstances of significant binding to plasma proteins.

The in vivo sampling technique can be applied to other acute pharmacokinetic studies for which the plasma concentration-time integral can be of use.

Major Findings: During the present fiscal year, prototype sampling systems have been designed and fabricated. Preliminary evaluation is under way to determine the appropriate membranes to use in the various applications and to refine the geometry and operating conditions for the membrane modules. Membranes in both shunt and hollow fiber configurations are being investigated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10054-01 BE

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Biomechanical Study of the Impairment of Wound Healing as a Consequence of a Variety of Cancer Therapies.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	J. Boretos	Chemical Engineer	ChES BEIB DRS
	D. Devereaux	Clinical Associate	SURG. NCI
	M. Brennan	Senior Scientist	SURG. NCI

COOPERATING UNITS (if any)

SURG., NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Clinical impression suggests that Adriamycin interferes with wound healing. Biomechanical and biochemical studies of wound healing in the rat have been undertaken. Thus far, we have shown that wound breaking strength is significantly reduced when adriamycin accompanies surgery up to three days post-op. Delaying administration of adriamycin by seven days post-op eliminates the deleterious effect.

It appears that the defect contributing to reduced wound breaking strength in adriamycin treated animals is not due to a collagen maturation defect but is due to a reduction in scar collagen accumulation as measured by "new" hydroxyproline content and reduced fiber diameter as determined by EM measurements.

ZO1 RS 10054-01 BEI

Objectives: To study effects of a variety of cancer therapy protocols on wound healing, and to attempt to elucidate the underlying mechanism of any such deleterious results.

Methods Employed: Biomechanical studies are both analytical and experimental in nature. Tissue stress-strain relationships are obtained from an Instron tensile testing machine. Biochemical determinations and electron microscopy are performed simultaneously with the biomechanics.

Significance: Results of the study may lead to modified clinical protocols with the intention of promoting wound healing, thereby improving post-operative recovery.

Proposed Course: To study in detail the constitutive behavior of the healing wound.

Publications:

Devereaux, D.F., Thibault, L., Boretos, J., Brennan, M.F.: The quantitative and qualitative impairment of wound healing by Adriamycin. Proc. of Soc. og Surg. Onc., April 2-6, 1978, San Diego, CA.

Devereaux, D.F., Thibault, L., Boretos, J., Brennan, M.F.: The quantitative and qualitative impairment of wound healing by Adriamycin. Cancer (In Press).

Devereaux, D.F., Thistlethwaite, P.A., Thibault, L.E., Brennan, M.F.: Effects of tumor bearing and protein depletion on wound breaking strength in the rat. Cancer (In Press).

Devereaux, D.F., Triche, T.J., Webber, B.L., Thibault, L.E., Brennan, M.F.: A study of adriamycin reduced wound breaking strength in rats: An evaluation by light and electron microscopy, induction of collagen maturation and hydroxyproline assay. Cancer (In Press).

FED. AGY. FOR SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10055-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Breath by Breath Analysis of Computer Controlled Exercise Stress Testing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	T. Talbot	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer (Tech.)	ACES BEIB DRS
	R. Winslow	Sr. Scientist	IR-CL-NHLBI

COOPERATING UNITS (if any)

IR-CL-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)

[X] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [ ] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In recent years exercise stress testing has become an important diagnostic tool. Most testing of this type is confined to cardiac studies. This system has been developed in order to assess the ability of the subject to transport and exchange oxygen and carbon dioxide between the atmosphere and the cells of the body. A large number of pathophysiologic states limit one's ability to perform these functions efficiently. With this system the anaerobic threshold of the subject during exercise can be detected non-invasively by breath-by-breath respiratory analysis. Oxygen Uptake, Carbon Dioxide Production, Respiratory Minute Volume, Respiration Rate, Heart Rate, and Respiratory Quotion are displayed as a function of Work Rate.

Z01 RS 10055-01 BEI

Objectives: To develop a system to analyze the respiratory quotient vs. work rate curve during exercise stress testing in order to determine the anaerobic threshold.

Methods Employed: A Tektronix 4051 programmable calculator and custom designed synchronous integrators and multiplexor has been used to produce breath-by-breath analysis of respiratory quotient as a function of work rate.

Significance: Correlation of the onset of anaerobic metabolism with work level provides a useful clinical measure of the general condition of the hematology patients under study. This method provides a better means of evaluating the efficacy of therapeutic measures.

Proposed Course: To add a pressure transducer to the mouthpiece in order to obtain respiratory power and work.

FIC: ... SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (DO NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10056-01 B

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Ultrasonic Visualization of Tongue During Speech

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	B. Sonies	Speech Therapist	CC
	T. Shawker	Staff Radiologist	CC
	T.E. Hall	Electronics Engineer	ACES BEIB DRS

COOPERATING UNITS (if any)

CC, NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.2	.1	.1

CHECK APPROPRIATE BOX(ES)

[X] (a) HUMAN SUBJECTS [ ] (b) HUMAN TISSUES [ ] (c) NEITHER

[ ] (a1) MINORS [ ] (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A two-dimensional ultrasonic sector scanner is being employed to visualize a mid-sagittal section of the tongue in human subjects during speech. Normals and individuals with various articulatory dysfunction will be compared.

Objectives: To determine if ultrasound is a useful diagnostic tool for speech disorders or for speech research.

Methods Employed: A mechanical ultrasonic sector scanner is held under and behind the chin of the subject, scanning upward in the mid-sagittal plane. A T.V. monitor displays the profile of the top of the tongue, and the real time images are recorded on videotape for later analysis. A normal T.V. camera simultaneously records a front and side view of the subject's face to correlate lip motion and transducer placement with tongue position. An audio recording is also made simultaneously.

Major Findings: The apparatus has been built and experiments will soon begin.

Significance: If results are positive, ultrasound may be shown to be a useful diagnostic and research tool, perhaps permitting quantitative differential diagnosis of a few speech disorders not easily done by other means.

Proposed Course: Data will be collected and analyzed.

FEDERAL RESEARCH INFORMATION EXCHANGE PROJECT NUMBER (DO NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10057-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Development of NMR Imaging Magnet

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	D. Hoult	Electrical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	.7	.8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A novel magnet suitable for nuclear magnetic resonance (NMR) imaging has been designed, and constructed. The magnet employs windings on two hemispherical shells which can be rotated with respect to each other about two orthogonal axes. This arrangement allows prescribed large gradients in magnetic field to be superimposed on an initially homogenous field. The magnet will consume 10 kw of power and has an inner spherical diameter of 0.6 m.

Z01 RS 10057-01 BEI

Objectives: To provide a large scale magnet suitable for exploring medical application of NMR imaging. The size of the device will permit examination of babies for detecting fluid filled lesions.

Methods Employed: A magnet consisting of two hemispherical shells each containing two separate windings has been developed. The shells are aluminum coatings of 0.67 m diameter with radial flanges projecting out from their surface. Approximately 400 kg of 0.37 cm square copper magnet wire is wound on each shell between the flanges. The shells can be tilted with respect to each other about two orthogonal axes to produce strong magnetic field gradients. This is accomplished by supporting the hemispherical shells on matching sections of spherical bearings mounted on a pair of support cradles. Leadscrews provide the force needed to tilt the massive device. The magnet dissipates 10 kw which is removed by water flowing in copper tubes attached to the inside of the shells.

Design goals are a homogenity of one part in 10^6 for the axial magnetic field when there is no tilt, and a uniform gradient producing a maximum variation of 1½% of the magnetic field at a 5 cm radius for maximum tilt. The castings and large spherical bearings have been fabricated to a nominal overall accuracy of less than 0.075 cm and $\frac{1}{2}^{0}$.

Significance: The above described magnet is one of several essential components of a novel NMR imaging system being developed for a variety of diagnostic applications.

Proposed Course: Complete construction of magnet and auxillary cooling system. Test field for homogeniety, uniformity of gradients, long-term stability, and repeatability. Make necessary field corrections required to meet design specifications.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10058-01 BEI

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Analytical High Voltage Electron Microscopy and Image Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.E. Fiori	Physical Scientist	BEIB DRS
OTHER:	A. Leroy	Physical Chemist	BEIB DRS
	E. Silbergeld	Neurotoxicologist	ETB IRP NINCDS
	J.L. Costa	Staff Physician	CNB NIMH
	K.E. Gorlen	Electronics Engineer	DCRT DRS
	E. Pottala	Electronics Engineer	DCRT DRS
	C. Swyt	Physicist	NHLBI LEA
	W. Bonfield	Pathologist	NCI

COOPERATING UNITS (if any)

NINCDS; NIMH; DCRT; NHLBI; NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Considerable effort was expended in establishing the specifications for the high voltage electron microscope and ancillary support equipment. A microscope satisfying our requirements has been delivered. It is a 200KcV Hitachi H700H equipped with an electron energy loss spectrometer and a lithium-drifted silicon energy dispersive X-ray detector. It is the first commercial instrument of its kind. The principal ancillary equipment purchased consists of a complete photographic darkroom to process the microscope plates and a PDP 11-60 computer to automate the microscope and perform the required data reductions and image analysis. The involved checkout procedures and acceptance tests of the microscope and its accessories are in progress. The electronic design of the computer interface and purchase of necessary components is in progress. The extensive software required will be designed and written later in this report period. The two additional personnel required to staff the project have been selected and the hiring process has been initiated. Design of the initial experiments is in progress. It is anticipated that some preliminary experimentation, in collaboration with selected researchers from other institutes could begin toward the end of this reporting period.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10059-01 BEI

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Automated Scanning Electron Beam X-ray Microanalysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.E. Fiori	Physical Scientist	BEIB DRS
OTHER:	A. Leroy	Physical Chemist	BEIB DRS
	K.E. Gorlen	Electronics Engineer	DCRT DRS
	E. Pottala	Electronics Engineer	DCRT DRS
	D.L. Fry	Medical Doctor	NHLBI LEA

COOPERATING UNITS (if any)

DCRT; NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This is a new project for which the principal instrumentation, the Scanning Electron Beam Microprobe, will not be delivered until the next reporting period. The bulk of the work expended on this project to date has been in the evaluation and establishment of specifications of the instrument. The microprobe chosen is a Cameca MBX, 2-50MeV, two wavelength spectrometer machine. The expected delivery will be in January, 1980. Preliminary electronic design of the computer interface has been accomplished. The principal investigator on this project has an extensive background in electron beam microanalysis applied to problems in materials science. He has been attending meetings and seminars germane to biological applications. Dr. Leroy, for this entire reporting period, has been on a training assignment in Orsay, France, acquiring the appropriate background in preparative techniques and in interpretation of results obtained by electron beam microanalysis.

Fiori, C.E. and Myklebust, R.L. "A simplex method for fitting Gaussian profiles to x-ray spectra obtained with an energy-dispersive detector". Journal of the American Nuclear Society, in press.

Fiori, C.E., Myklebust, R.L., and Newbury, D.E. "A catalogue of artifacts observed in energy dispersive X-ray spectrometry and their influence on analysis". NIH-Sponsored Special Workshop on Electron Column Instrumentation in Biology, Proceedings in Press, Academic Press.

Swan, A., Fiori, C.E., and Heinrich, K.F.J. "Daguerreotypes: The Plates and the Process". Scanning Electron Microscopy, 1979.

Heinrich, K.F.J., Fiori, C.E., and Myklebust, R.L. "Relative transition probabilities from the K-state". Journal of Applied Physics, in press.

Fiori, C.E. "Energy Dispersive Detectors: A bibliography". Proc. of the Micro. Analy. Soc., 1979.

VRB Special Project Reports

1978-79 DRS ANNUAL REPORT

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00001-09 VR

PERIOD COVERED
October 1, 1978 - September 30, 1979

TITLE OF PROJECT (80 characters or less)

Animal Model Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I: C.T. Hansen	Geneticist	VRB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
Division of Research Services, NIH, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The program is concerned with animal model development and specifically those which have a direct application to human disease. The major emphasis is on those systems which define the immune system. The ultimate goal is developing a mouse system which is deficient in T-lymphocytes, B-lymphocytes, macrophages and natural killer cell (NK) activity. In turn, each one of these defects may be reintroduced into the immunodeficient mouse to study the role of these components of the immune system, either singly or in combination, in bringing about immune responses to neoplasms, parasites and bacterial infections. In addition, a program is underway to also explore the role of gene A^{vy}, which has a major physiological effect in the expression of neoplasms in combination with the above immunologically defined mice.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: To develop animal models for biomedical research utilizing the resources of National Institutes of Health Genetic Resource.

Methods Employed: The use of appropriate mating systems combined with continuous physiological monitoring to yield the desired model.

Major Findings: Recent results show that human tumors which would not grow or grew very poorly in mice deficient in T-lymphocytes only can be successfully transplanted into mice deficient in both T and B-lymphocytes.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 00002-08 VR

PERIOD COVERED
October 1, 1978 - September 30, 1979

TITLE OF PROJECT (80 characters or less)

Development of Diets for Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.J. Knapka	Nutritionist, SAS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
Division of Research Services, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A continuing program in laboratory animal nutrition involves various stocks and strains of guinea pigs, rats, and mice maintained in conventional and specific pathogen-free environments. This program utilizes a series of factional-designed feeding trials to evaluate the effect of either varying nutrient concentrations or different dietary ingredients on growth, reproduction, and maintenance of the various species. The objective of this program is to develop open formula natural ingredient diets for these species so the nutritional status of production and research animal colonies can be improved. Data generated by this program are used as a basis for estimating the nutrient requirements of the species involved and also for ascertaining differences in nutrient requirements for stocks or strains within a species.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: To improve the status of NIH production and research colonies of laboratory animals by identifying the quantitative nutrient requirements of specific species and providing open formula diets containing the required nutrient concentrations. To identify potential differences in nutrient requirements among stocks and strains of small laboratory animals and during the various phases of their life cycle - growth, reproduction and maintenance. To provide NIH investigators with modifications of open formula diets to accommodate specific research projects.

Methods Employed: A series of factorial designed feeding trials are conducted to ascertain the effect of varying dietary concentrations of nutrients or different feed ingredients on growth, reproduction and maintenance of rats, mice or guinea pigs maintained in conventional or specific pathogen-free environments. Criteria of evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, preweaning mortality, weight of offspring weaned and the postweaning growth of offspring. Diets for maintenance are evaluated by determining longevity. Methods for improving diet palatability are also evaluated. Data from all studies are coded for computer analysis by the appropriate statistical methods.

Major Findings: This program has developed open formula diets for all animal species maintained by the Small Animal Section. These diets are somewhat different in nutrient concentrations than commercially available diets in that they provide nutrients at concentrations nearer the estimated animal requirements. Differences have also been shown in the nutrient requirements among different species of mice. Data obtained from a study involving a purified diet indicate mice will reproduce as well on this kind as on natural ingredient diets.

Significance: The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved when diets supply nutrient concentrations equal to the actual requirements of the animal species involved. Diets formulated to accommodate specific research projects, or standard diets, provide NIH investigators and the scientific community with an essential research tool when experimental data are to be verified by replicating experiments. The use of open formula diets for large animal colonies also results in a considerable economic advantage for colony maintenance.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00004-18 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Tyzzer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. R. Ganaway	Chief, Microbiology Unit	CPS VRB DRS
OTHER:	T. H. Spencer	Microbiologist	CPS VRB DRS
	A. M. Allen	Chief, CPS	CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.3	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The continuing purpose of this project is the study of Tyzzer's disease. The topics of present interest are: (1) characterization of the causative agent, Bacillus piliformis, of which we presently have isolants from four animal species (rabbit, horse, rat and mouse) in pure culture; (2) the serological response of the host to B. piliformis infection and the serological relationship between isolants from different animal species using the complement fixation test and fluorescent antibody techniques; (3) the pathogenesis of Tyzzer's disease in various animal species; and (4) the epidemiology of Tyzzer's disease, the goal being to identify primary sources of the infection.

PHS-6040
(Rev. 10-76)

Objectives: To characterize the etiologic agent, B. piliformis; to study the pathogenesis, the immune response and mechanisms, and to develop means to present or control the disease.

Methods Employed: Microbiology, immunology and pathology.

Major Findings: Isolants from the mouse and rat originating from Dr. Fujiwara's laboratory in Japan (supplied as infected mouse liver by Charles River Breeding Labs, Wilmington, Massachusetts) have been isolated in pure culture in embryonated eggs, working pools prepared, and passage established in mice. Morphologically and culturally, they are similar but not identical to rabbit and horse isolants studied in this laboratory. Hyperimmune sera are being prepared in rabbits so that serological relatedness of these isolants can be determined. Logarithmic growth of B. piliformis (rabbit origin) was harvested and sent to Dr. John Johnson (Virginia Polytechnic Institute and State University, Blacksburg, Virginia) who offered assistance to determine the G + C content of the DNA of this parasite, a requisite to possible classification. Eleven strains of mice (10 inbred and NIH outbred) were tested for susceptibility to B. piliformis (rabbit origin), with and without exogenous cortisone. Infection was readily established and successfully passaged in each of the strains of mice provided they were given cortisone concurrently. In only one strain, CBA/N, was this possible without the aid of cortisone. The CBA/N mouse is deficient in I_gM.

Significance: Often occurring as an epizootic, Tyzzer's disease causes fatal disease in mice, rats, hamsters, gerbils, laboratory rabbits, guinea pigs, nonhuman primates, cats, dogs, horses, wild hares, cottontail rabbits, coyotes, and muskrats. The etiologic agent, a Gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. The disease occurs throughout the world and is one of the more important diseases of laboratory animals that interferes with and complicates biomedical research.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00008-05 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Neoplasia in the Nude Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Chief, Pathology Unit	CPS VRB DRS
OTHER:	C. T. Hansen	Geneticist	SAS VRB DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Discontinued because data has been published by other investigator.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00011-05 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Effect of Season on Pituitary and Gonodal Hormone Levels in Adult Male Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief, VMSS	VRB DRS
	G.D. Hodgen	Chief, ES	RRB NICHHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	.25	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to assess the seasonal changes in endocrine parameters important in male fertility. Measurements of androgens measured as a biorhythm will be correlated to breeding efficiency and season.

PHS-6040
(Rev. 10-76)

Objectives: In most studies of infertility, the major emphasis of investigation is on the female. This study encompasses a longitudinal analyses of fertililty in the male rhesus monkey, Macaca mulatta, to investigate cyclic patterns of spermatogenesis.

Methods Employed: Ten male breeder monkeys were bled the first five days of each month for a 12-month period. Follicle-stimulating hormone, luteinizing hormone, testosterone, and androsterone were assayed using sensitive radioimmunoassay methods. The results were correlated with time of month, season, and breeding efficiency. Currently, radioisotope analyses of serum are being repeated.

Significance: Fertility and sterility studies focusing on male endocrine parameters have not been extensive. Approaching male endocrine changes as a biorhythm may lead to basic understanding of reproductive endocrinology. In addition, our results may be applied directly to biomedical research to improve nonhuman primate breeding, which is important because large-scale domestic colonies are a major resource to the scientific community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00012-05 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Hormone Levels During the Postpartum Interval in Nursing and Nonnursing Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.K. Johnson	Chief, VMSS	VRB DRS
	G.D. Hodgen	Chief, ES	RR NICHHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	.05	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The interval from delivery to the first fertile menstrual cycle in rhesus monkeys (Macaca mulatta) is not known. Breeding management requires such information to maximize the use of breeder males for space management planning and efficiency in timed-mating protocols. Serum levels of various gonodal hormones will be measured to identify the onset of menstrual cycles in which ovulation occurs.

PHS-6040
(Rev. 10-76)

Objectives: The most effective contraceptive mechanism among women in developing countries is lactation. The birth time interval is directly related to the lactation period in nursing mothers. This study will use the rhesus monkey as a model to examine hypothalmic-pituitary (H-P) systems influencing the onset of ovulation after birth.

Methods Employed: Seven nursing rhesus monkey mothers and seven nonnursing mothers will be bled for 90 days beginning one day after delivery. Serum levels of follicle-stimulating hormone, leutinizing hormone, estradiol, and progesterone were measured to identify the onset of ovulatory menstrual cycles.

Major Findings: During gestation a transient "lesion" develops in the H-P system and persists into the puerperium. It blocks the positive feedback response of surge gonadotropin secretion induced by estradiol. However, this H-P failure is not sufficient by itself to explain postpartum infertility in these primates since, in nonnursing monkeys, spontaneous resumption of ovulatory menstrual cycles seldom occurs until 2-4 months after delivery at term.

Significance: Development of domestic breeding colonies of rhesus monkeys for biomedical research requires better understanding of their reproductive physiology leading to improved fertility and management practices. Our results provide endocrine parameters as a model for reproductive endocrinology in women.

Proposed Course: Project completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00014-05 VR

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Evaluation of Efficacy of M. bovis PPD Tuerculin in Detection of Tuberculosis in Wild-caught Indian Rhesus Monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.M. Renquist	Head, PQU	VRB DRS
OTHER:	M.L. Morin	Veterinarian	VRB DRS
	D.W. Johnson		U. of Minnesota
	L. Conyha	Staff Veterinarian	USDA
	C. Thjoen	Head, Mycobacteriology	USDA

COOPERATING UNITS (if any)

Veterinary Services Laboratories, Mycobacteriology Section, APHIS, USDA, Ames, Iowa
Dept. of Veterinary Clinical Sciences, U. of Minnesota, St. Paul, Minnesota

LAB/BRANCH

Veterinary Resources Branch

SECTION

Animal Center Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A comparison of the immune response to PPD (0.6-6.5 mg/ml protein) and MT (mammalian tuberculin-USDA reference strength) using natural cases of primate tuberculosis is being determined. Results indicate the hypersensitivity response with MT is linear, increasing with the amount of protein present. The hypersensitivity response with PPD is not linear, plateauing at approximately 2.0 mg/ml. The response with MT was consistently of greater intensity than PPD using equivalent strengths above 0.6 mg/ml of protein. MT appears to be a better product for diagnosing tuberculosis in rhesus monkeys.

PHS-6040
(Rev. 10-76)

Objectives: Intradermal tuberculin testing in nonhuman primates is done primarily with commercially prepared USDA mammalian tuberculin (MT). This study compared the efficacy of M. bovis purified protein derivative (PPD) with MT. Clinical pathology and immunologic parameters of primate tuberculosis are also being studied.

Methods Employed: Comparisons of MT and PPD are being made using equivalent concentrations, calculated according to the amount of protein in each product. The only exception is with eyelid intradermal testing which compares various concentrations of PPD to full strength mammalian tuberculin (FSMT). Test animals are selected from natural reactors during the quarantine period. Reactors are caged with healthy monkeys which are then tested at weekly intervals for conversion.

Major Findings: MT was found to be the most efficient product for diagnosis of tuberculosis in primates because 1) the delayed hypersensitivity reaction intensity (HRI) was greater without comparing 2 mg/ml PPD to equivalent concentrations of MT, 2) the positive or suspectHRI to MT was elicited up to three weeks prior to those with PPD, 3) the maximum HRI to PPD plateaued near 2 mg/ml concentration with HRI increasing very little with concentrations almost two times that of MT, and 4) the HRI in rhesus is a cyclic reaction requiring the strongest product to elicit HRI at the low periods of the cycle.

Significance: The study permits the evaluation of the most effective product for detection of tuberculosis in naturally exposed nonhuman primates.

Proposed Course: Completed. A manuscript is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00015-04 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Defining the Nude Mouse Model

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.A. Whitney, Jr.	Chief	VRB DRS
Others:	C.T. Hansen	Geneticist	VRB DRS
	J.R. Ganaway	Chief, MU, CPS	VRB DRS
	A.M. Allen	Chief, CPS	VRB DRS
	H.J. Alter	Blood Bank	CC
	P. Holland	Blood Bank	CC
	R. Purcell		LID NIAID

COOPERATING UNITS (if any)
Laboratory of Infectious Diseases, NIAID
Blood Bank, Clinical Center

LAB/BRANCH
Veterinary Resources Branch

SECTION
N/A

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15	0.05	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The nude mouse CBA congenic backcross is now available for further investigations on susceptibility of this to three forms of human viral hepatitis. This year a pilot study was initiated exposing the CBA nude to filtrated stool containing the antigen of human hepatitis A. Rapid death in all inoculated animals ensued, most likely due to an endotoxin in the fecal filtrate. Additional pilot studies with hepatitis A are now being planned. Hepatitis B and hepatitis non-A, non-B will also be inoculated into these mice during the summer of 1979.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00016-03 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Characterization of a New Viral Disease of Rabbits

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.D. Small	Animal Disease Investigator	VRB DRS
OTHER:	R.A. Squire		Johns Hopkins University
	L. Aurelian	Virologist	Johns Hopkins University
	J.D. Strandberg	Pathologist	Johns Hopkins University

COOPERATING UNITS (if any)
Johns Hopkins University School of Medicine, Baltimore, Maryland

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The initial phase of this project has been completed. The virus has been identified as a coronavirus which reacts with human coronaviruses OC 43 and 229E. The virus causes lesions in the cardiac muscle (Cardiomyopathy) leading to right-sided failure and pulmonary edema. Rabbits, but not mice, hamsters, or guinea pigs are affected. Natural spread of the infections was not recognized. Results have been published.

Further work has been suspended pending availability of space.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00019-03 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Aging Studies on HSR-Stroke/Prone Rats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Chief, Pathology Unit	CPS VRB DRS
OTHER:	C. E. Hunt	Veterinary Pathologist	U. of Alabama

COOPERATING UNITS (if any)
None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to determine the nature and incidence of pathology lesions that develop throughout the life span of HSR/stroke prone rats. WKY rats will be used as controls. Animals of each sex will be examined at 3 months & months, 9 months, 12 months and 15 months of age. Tissues will be studied by light microscopic methods and if indicated, electron microscopic technique. These strains have great potential as animal models for the study of cerebrovascular disease in human beings.

This study involves only HSR/SP rats, so a new title was inserted to reflect that change.

PHS-6040
(Rev. 10-76)

Objectives: To determine the nature and incidence of pathologic lesions that develop throughout the lifespan of HSR-stroke prone rats. HSR-stroke prone rats are reported to be hypertensive, +140 mm Hg, but a pathologic study of the strain apparently has not been made. The HSR-stroke prone rat is reported to spontaneously develop cerebral infarcts, although documentation is sketchy. The WKY is the parent strain of the HSR and HSR-stroke prone rats and will be studied as a control.

Methods Employed: Animals of each sex will be selected for long-term holding. Aliquots will be killed at 3 months, 6 months, 9 months, 12 months and 15 months of age. Tissues will be studied by light and if indicated electron microscopic methods. Pathology will be correlated with lipoprotein and plasma triglyceride levels. WKY rats will be used as controls.

Significance: This strain has great potential as an animal model for the study of cerebrovascular and hypertensive disease in humans. Its value depends on accurate pathological description and documentation.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00020-03 VR

PERIOD COVERED

October 1, 1978 to February 1979

TITLE OF PROJECT (80 characters or less)

Intrautero Injection of Herpes saimiri and Epstein-Barr Virus in Pregnant Guinea Pigs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. W. Pearson	Head, VIS	LRTV NCI
	J.D. Bacher	Chief, SU, VMSS	VRB DRS

COOPERATING UNITS (if any)

National Cancer Institute

LAB/BRANCH

Veterinary Resources Branch

SECTION

Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies have continued toward the development of a guinea pig model to study Epstein-Barr Virus (EBV), a virus implicated in human cancer, and Herpes saimiri (HVS), a virus known to transform human cells in vitro. Chronically infected pigs have consistently exhibited serum antibodies to EBV and HVS as judged by immunofluorescence. Tumor promoting agents, such as procarbazine and TPA, have been injected into these animals to promote the carcinogenic activity of these viruses.

PHS-6040
(Rev. 10-76)

Objectives: The aim of this project is to study two primate oncogenic viruses, Epstein-Barr (EBV) and Herpes saimiri (HVS), with regard to infectivity and their transforming potential in vivo in guinea pigs and in various populations of guinea pig cells. In vitro techniques have been employed to follow vial infection based on antibody responses in guinea pigs inoculated with EBV or HVS.

Methods Employed: 1) Inoculation of fetal guinea pigs (20-40 days gestation) with EBV and HVS; 2) inoculation of the same guinea pigs after birth with EBV and HVS; 3) cardiac, intraperitoneal, and bone marrow inoculation of newborn guinea pigs; 4) treatment of guinea pigs with guinea pig antithymus serum, procarbazine, and TPA; and 5) Use of indirect immunofluorescence to monitor guinea pigs infected with EBV and HVS for humoral antibodies against associated antigens.

Major Findings: Chronically infected guinea pigs have consistently exhibited serum antibodies to EBV (Viral Capsul Antigen (VCA) 1:10 to 1:160; Early Antigen (EA) 1:10 to 1:40) and the HVS (VCA 1:20 to 1:80; EA 1:10 to 1:20) as judged by indirect immunofluorescence. Following the administration of procarbazine (100 mg/kg) plus TPA (1 μg/kg) weekly for 10-15 weeks to a number of chronically infected EBV and HVS pigs, a high percentage of the animals came down with fulminating leukemia. In contrast, infected animals (EBV and HVS) exposed to either drug alone have shown no signs of disease at the moment. Likewise, normal animals adminstered a similar regimen of procarbazine or TPA alone or in combination have remained in a healthy state. Imprints prepared from tissues removed from the EBV infected animals all exhibited an antigen indicative of viral infection. Histological examination of tissues from animals (both EBV and HVS) that died from leukemia revealed an undifferentiated lymphatic leukemia. In vitro attempts to identify EBV and HVS as the causative agents of these leukemias such as the presence of viral antigens and co-cultivation techniques into susceptible cells have ben unsuccessful due to the inability to establish in vitro cell lines from tissues removed from leukemic animals. Serological studies have revealed that sera obtained from the EBV and HVS pigs near death have antibody also against the guinea pig herpes virus. It is felt that the guinea pig herpes virus expresses itself within 72 hours after tissue cells have been seeded, leading to the subsequent death of the cell lines.

Significance: The long-term goal of this project is to develop a guinea pig model to study EBV, a virus implicated in human cancer, and HVS, a virus known to transform human cells in vitro. Such a model system could provide evidence of the involvement of these two herpes viruses in the pathogenesis of neoplasia and serve as a definitive model for investigating measures for prevention and treatment of cancer in human beings.

Proposed Course: Discontinued because EBV and HVS virus cannot be isolated in tissue culture from guinea pig showing signs of leukemia. Also, the leukemia is not of the same type seen in man.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00022-03 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Skeletal Age Development in Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Comparative Anatomist, VMSS	VRB DRS
	W. Watson	Chief, SAS	VRB DRS
	R.L. Killens	Chief, CMU, VMSS	VRB DRS
	J.D. Bacher	Chief, SU, VMSS	VRB DRS
	N.R. Hayes	Deputy Chief, VMSS	VRB DRS
	D.K. Johnson	Chief, VMSS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	1.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The most widely used methods (dental age, body weight) for age estimation in nonhuman primates are inadequate. More precise standards and age indicators are needed and can be obtained by measuring skeletal age, which has proven to be the best criteria for assessment of chronological age. Our longitudinal radiographic studies will provide information on the development and bone maturation of the hand and wrist in Macaca mulatta monkeys. The data will cover the entire period of appendicular bone maturation, from 120 days of gestation (the onset of carpal center ossification) to adulthood (over five years). To obtain the fetal data, a novel surgical technique of multiple uterotomies was developed. Serial radiographic data are obtained at three uterotomies and after delivery. The pre and postnatal age indicators will be prepared for publication as an atlas, which should make the data readily usable in many studies where the precise age of the experimental animal is required.

PHS-6040
(Rev. 10-76)

Objective: To provide information on bone development and maturation of the hand and wrist in the rhesus monkey, Macaca mulatta. This information will be used for publication as an atlas and will serve as a comparison with human bone maturation.

Significance: Assessment of bone maturation by use of roentgenograms of the extremities is the best method for determining age. It provides age estimates throughout the developmental period and allows detection of experimentally induced variations in the skeletal development. Our data, obtained from normal fetuses, will be valuable for a variety of studies. The most important impact of it might be on experimental teratology and genetics, where rhesus monkeys of unknown age are widely used as models. It should constitute an important contribution to better understanding of prenatal development in Macaca mulatta. The data may also serve as a basis for comparison with human material in a variety of studies. Moreover, the success of the serial uterotomies may provide new possibilities for prenatal treatment of the human fetus, as for blood disorders when prenatal transfusion is needed but existing methods are risky; for skeletal disorders when early surgical treatment may be of great value; and, perhaps, for many other conditions that might be corrected by a surgical procedure before birth.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00024-03 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Anthelmintic Effect on Antibody Levels Following Primary and Secondary Immune Stimulation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. L. Morin	Chief, PRU, VMSS	VRB DRS
	G. D. Hodgen	Chief	ES NICHHD
	L. D. Stuart	Chief, UU, ACS	VRB DRS
	F. J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)
Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.01	.01	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine if anthelmintics (thiabendazole or leavamisole hydrochloride) interfere with the normal immune response. Sheep receiving primary or secondary immune stimulation are being routinely dewormed, and the circulating antibody responses determined. Preliminary results indicate that the anthelmintics do not affect antibody production.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if anthelmintics (thiabendazole and levamisole hydrochloride) interfere with normal immune response as measured by circulating antibody levels.

Methods Employed: Sheep receiving primary or secondary immune stimulation were routinely dewormed, and the circulating antibody responses determined. Sheep were separated into three groups, one for each anthelmintic and one for saline control.

Major Findings: Preliminary information suggests that the drugs do not affect circulating antibody levels.

Significance: Preliminary findings indicate that routine deworming practices do not affect the immunologic response of antibody-producing ruminants.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00026-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Subclinical Ascorbic Acid Deficiency in the Guinea Pig

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Chief, Pathology Unit	CPS VRB DRS
OTHER:	A. M. Allen	Chief, CPS	CPS VRB DRS
	J. D. Small	Veterinarian	SAS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Nine episodes of subclinical scurvy were investigated. Diagnosis was based on histological examination of the femoro-tibial articulation. Ascorbic acid is necessary for connective tissue and matrix formation. Therefore, osteoid trabeculae formation in the metaphysis of the tibia was used as an index of ascorbic acid. In guinea pigs with subclinical scurvy, there was a marked decrease in osteoid trabeculae formation without classical lesions of overt scurvy. Clinical histories of all episodes revealed poor food management practices. These included storage of food at abnormally high temperatures, improper formulation by the manufacturer and abnormally long periods of storage. Overt scurvy did develop as a sequel to subacute scurvy when adequate corrective measures were not taken. Purified ascorbic acid was given to the survivors and they recovered. We believe subclinical scurvy is a potential cause for major losses in guinea pig colonies, and that whenever significant losses are encountered without significant gross lesions, subclinical scurvy should be considered in the differential diagnosis.

PHS-6040
(Rev. 10-76)

Objectives: To report the occurrence of subclinical scurvy as a cause of morbidity and mortality in guinea pig colonies.

Methods Employed: Collect naturally occurring cases of subclinical scurvy, that is, cases where no overt gross lesions of ascorbic acid deficiency occur but causes considerable morbidity and mortality. Examine histologically all suspected animals and correlate findings with clinical history.

Significance: It is believed that subclinical scurvy is much more common in guinea pig colonies than is generally appreciated and that it is a major cause of animal losses. Our findings may increase awareness on the part of animal care personnel, clinicans and pathologists as to the potential for subclinical scurvy to cause serious health problems in guinea pig colonies.

Proposed Course: Objective achieved, study is discontinued.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00027-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Linkage Analysis in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
OTHER:	K. P. Smith	Geneticist	CPS VRB DRS
	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Bio Lab Tech	CPS VRB DRS

COOPERATING UNITS (if any)
Cell Surface Antigen Laboratory, Memorial Sloan-Kettering Cancer Center, New York, New York; NIAID; and University of Melbourne, Australia

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunological techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: To identify and locate on the chromosomes of the laboratory mouse genetic traits which can be used in a wide range of biomedical research areas.

Methods Employed: Analysis of proteins and enzymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic and immunofluorescence methods.

Major Findings: (1) Lymphocyte Cell Surface Antigens: (a) Ly-5 was located on chromosome 1 approximately 3 map units from the enzymes dipeptidase. A 4 point linkage test is being performed to determine the exact distance and gene order on this chromosome. (b) Preliminary data suggest that Ly-9 may be linked to glucose-6-phosphate dehydrogenase on chromosome 4. Additional backcross animals are being bred to verify this finding. (c) Studies to determine the chromosomal location of Ly-6 have been initiated. (2) Biochemical Markers: (a) A new allele (Mup-1c) of the major urinary protein in the mouse was detected and verified by backcross analysis. The type strains carrying this allele are both NIH strains, NGP and FVB. (b) A detailed linkage analysis is being performed to determine the exact distance of the enzyme catalase from the loci coding for the major histocompatibility complex and thymic leukemia antigens in the mouse. There is some suggestion that recombination may be suppressed in this critical region of the seventeenth chromosome.

Significance: Determination of the chromosome location of these inheritable markers would permit their use in the quality control program initiated by the Genetic Monitoring Laboratory. In addition, these findings are of interest to the biomedical community with regards to the genetic characteristics of normal and diseased status.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00028-02 VR

PERIOD COVERED
October 1, 1978, to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Histocompatibility Testing and Blood Grouping of Donor and Inbred Dogs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. J. Bass	Chief, CU	VRB DRS
OTHER:	T. L. Wolfle	Assistant Chief, CU	VRB DRS
	F. J. Judge	Chief, ACS	VRB DRS
	R. W. Bull	Director, Research Immuno-hematology and Serology Lab	Michigan State

COOPERATING UNITS (if any)

Department of Medicine, Michigan State University, East Lansing, Michigan

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Histocompatibility studies of blood donor and inbred dogs are being conducted to correlate chronic health problems with genetic and tissue antigen types. Results are being used to evaluate inbreeding progress, match breeding pairs, and possibly correlate histocompatibility to puppy mortality. The NIH canine blood donor colony is also being studied to more fully characterize canine tissue antigens and blood groups and delineate potential rare types.

PHS-6040
(Rev. 10-76)

Objective: The objective is to determine if histocompatibility and blood group types are important genetic factors in chronic health problems and can be used to guide the inbreeding of dogs.

Methods Employed: Leukocytes are being used in mixed lympocyte cultures, in determinations of cell antigens, and in lymphoblastogenesis tests. Erythrocytes are being used for blood grouping into eight or more major and minor Dog Erythrocyte Antigen types.

Significance: It has been documented in man that certain tissue types are more commonly associated with particular diseases. If this also occurs in diseases of the dog, animals with defined tissue types can be useful as models of human disease. The study will promote understanding of canine diseases, etiologic investigations of chronic health problems in dogs, and development of a more productive colony. The tissue and blood type data will help refine the inbred dogs so as to provide a better standardized model for research.

Proposed Course: Typing is now in progress. Results will be analyzed for correlations with chronic health problems. Histocompatibility types are being used to determine breeding pairs and obtain true inbred dogs at a faster rate.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00029-02 VR

PERIOD COVERED
October 1, 1978, to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Clinical Pathology Studies of Animal Health Conditions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. J. Baas	Chief, CU	VRB DRS
OTHER:	T. L. Wolfle	Assistant Chief, CU	VRB DRS
	L. D. Stuart	Head, UU	VRB DRS
	N. Jackson	Veterinarian, ACS	VRB DRS
	F. J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are being conducted to define and characterize spontaneous clinical diseases occurring in the NIH ungulate herds and dog colonies. Preliminary clinical investigation has identified some disease problems. Hematological, bacteriological, and chemical tests are being made. The purposes of the investigations are to improve the quality of animals and animal products and characterize models of disease.

PHS-6040
(Rev. 10-76)

Objective: The objectives are to identify causes of diseases in NIH herds and colonies, help determine the pathogeneses, improve the quality of animals and animal products provided, and characterize models of disease.

Methods Employed: Several standard hematological, bacteriological, and chemical procedures are being employed at the Animal Center and through commercial laboratories. When an unusual technique or information is needed, assistance is enlisted from various institutions.

Major Findings: Johne's disease in goats has not been controlled through a culture test and slaughter method. Thus, a vaccination program has been instituted. The findings in the canine blood donor colony indicate that iron deficiency is important in some dogs but other deficiencies such as vitamin deficiencies have major contributory roles.

Significance: It is necessary to identify the disease problems and control or eliminate them to provide improved animals and products for biomedical research. Complete characterization of some conditions may provide models of human conditions, or help illustrate the pathogenesis of animal conditions.

Proposed Course: Pilot studies and incorporation of recent knowledge and methods are being used to determine a more definitive study.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00030-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Evaluation of Mycobacterium paratuberculosis Bacterin in the Goat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Chief, PRU, VMSS	VRB DRS
	L.D. Stuart	Chief, UU, ACS	VRB DRS
	R. Merkal	Research Veterinarian	NADL

COOPERATING UNITS (if any)

National Animal Disease Laboratory, Agriculture Research Services, Ames, Lowa

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section and Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is designed to determine if a bacterin against Johne's disease will affect the incidence and age of onset of the disease in goats. One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age and observed for life.

Objectives: The objective is to determine if a bacterin against Johne's disease will affect the incidence and age of onset of the disease in goats.

Methods Employed: One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age with a whole-cell bacterin against Mycobacterium paratuberculosis. The other half (in most cases the twin) will be used as a control. The animals will be housed on contaminated pastures and will serve as usual in NIH programs. Animal cultures will be prepared to check for M. paratuberculosis. At the end of their usefulness or when they develop clinical Johne's disease, the goats will be necropsied and their Johne's disease status evaluated.

Major Findings: Findings will not be known until 1982.

Significance: With the use of a bacterin, it may be possible to prevent or delay the onset of Johne's disease in goats, as it is in cattle, thus enhancing the usefulness of goats in research.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00031-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Serum Hormone Levels in Feral Pregnant Rhesus Monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.L. Morin	Chief, Pru, VMSS	VRB DRS
	D.M. Renquist	Chief, PQU, ACS	VRB DRS
	G.D. Hodgen	Chief, ES	RRB NICHHD

COOPERATING UNITS (if any)
Endocrinology Section, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section and Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.01	.01	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to observe the changes in reproductive hormone levels in feral pregnant rhesus monkeys. These changes may explain the high incidence of aboration during the first month of quarantine. Also, information on hormone levels during gestation in feral rhesus monkeys will be compared with data obtained from laboratory-bred monkeys.

PHS-6040
(Rev. 10-76)

Objective: The objective is to observe the changes in reproductive hormone levels in feral pregnant rhesus monkeys.

Methods Employed: Adult female rhesus monkeys are examined for pregnancy when they arrive at our facilities. Pregnant animals are bled three times per week until the pregnancy is terminated by abortion or parturition. Estrogen and progesterone levels are measured in each serum sample.

Significance: The results may explain the high incidence of abortion during the first month of quarantine. The hormone levels of feral rhesus monkeys during gestation will be compared with similar data from laboratory-bred rhesus monkeys.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00032-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
The Effect of Dietary Crude Fiber on the Digestibility of Proteins, lipids, and Carbohydrates in Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Barnard	Biol. Lab. Tech.	VRB DRS
OTHER:	D.M. Renquist	Chief, PQU, ACS	VRB DRS
	M.L. Morin	Veterinarian	VRB DRS
	J. Knapka	Nutritionist, SAS	VRB DRS

COOPERATING UNITS (if any)
Small Animal Section, VRB, DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine the digestibility coefficients of lipids, proteins, and carbohydrates as affected by different levels of crude fiber in monkey diets. The study involves comparing baked, 7 percent crude fiber diet to baked and extruded, standard 3 percent diets. The feces from 12 monkeys fed the three diets were collected and sent for laboratory analysis and determination of the digestibility coefficients.

PHS-6040
(Rev. 10-76)

Objectives: The purpose of the study is to determine the digestibility coefficients of lipids, proteins, and carbohydrates as affected by different concentrations of crude fiber in the nonhuman primate diets.

Methods Employed: Twelve rhesus monkeys, acting as their own controls, were fed experimental baked diets containing 2.9 percent and 5.6 percent crude fiber and a commercial extruded diet containing 2.4 percent crude fiber. The feed intake and fecal output were determined. The feces were analyzed to determine the digestibility coefficients.

Major Findings: Results indicate that the dietary crude fiber concentration used had no significant effort on the digestibility of crude protein, crude fat, no nitrogen-free extract. Crude fiber digestibility was significantly different from baked versus extruded diets. Statistical analysis of the digestibility coefficients is presently being finalized. Further data will be available.

Significance: This study follows up the Dietary Fiber Level Study (Z01 00023-01 VR). It is important to understand what portions of the crude fiber (carbohydrate and lignin) are digestible and how varying the crude fiber level affects the digestibility of lipids, proteins, and other carbohydrates.

Proposed Course: The measurement of the fecal transit times for the three diets will be finalized in the near future.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00033-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Application of Automatic Data Processing to Nonhuman Primate Colony Management

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.M. Renquist	Chief, PQU	VRB DRS
Others:	R. Van Wey, Jr.	MAO	OD DRS
	P. Basa	Computer Programmer	DCRT

COOPERATING UNITS (if any)
Division of Computer Research and Technology

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A system is being developed to computerize basic information obtained from nonhuman primates during the quarantine period. The system will be used to provide clinical histories, morbidity/mortality data, drug treatment effectiveness and other information on either a colony or an individual basis. The system will ultimately be able to provide intramural research investigators with a complete clinical profile on monkeys entering the PQU at NIH.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to computerize basic information obtained from nonhuman primates during the quarantine period.

Methods Employed: All routine background information including daily clinical history, diagnosis, and treatment data is computer printed on forms. After issue of the animal the form is key punched and the data is stored for computer retrieval.

Major Findings: All data has been placed in a historical archive file. Quarterly morbidity/mortality reports are received by disease, treatment, and cause of death. Epidemiologic and informational surveys on drug efficacy and disease spread can be provided.

Significance: The system will be used to provide clinical histories, morbidity/ortality data, drug treatment effectiveness and other information on either a colony or individual basis.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00034-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Reproductive Physiology of Selected Exotic Nonhuman Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.M. Renquist	Head, PQU	VRB DRS
	M.L. Morin	Veterinarian	CRB DRS
	Dennis Barnard	Biol. Lab. Tech.	VRB DRS
	Gary Hodgen	Chief, ES	NICHHD
	T.L. Wolfle	Asst. Head, CU	VRB DRS

COOPERATING UNITS (if any)

Endocrinology Section, RRB NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to establish breeding system for producing healthy, Aotus, Saimiri, Saguinus, and Cercopithecus animals in a consistent manner for research investigators at NIH and other interested scientists. Basic reproductive parameters being studied include duration of gestation, male and female productive cycles, relationships of accessory sexual organs to sexual activity, male-female breeding rations, reproductive hormone serum levels, puberty changes, infant development, and minimum reproductive age.

PHS-6040
(Rev. 10-76)

Objective: The objective of the study is to establish breeding systems for producing healthy exotic nonhuman primates.

Methods Employed: Data will be collected for the following parameters: a) duration of gestation, b) male and femal reproductive cycles, c) relationships of accessory sexual organs to sexual activity, d) male to female breeding ratios, e) reproductive hormone serum levels, f) puberty changes, g) infant development, and h) minimum reproductive age.

Major Findings: Weights and measurements are being performed weekly on every owl monkey born to establish indices for normal development. To date ten animals are on the study. Weights at 6 months of age are between 402 and 563 grams, approximately one-half that of the adult. Deciduous tooth eruption patterns are similar to other nonhuman primates.

Significance: This study will increase reproductive information to provide effective laboratory rearing of exotic nonhuman primates.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00035-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Developmental Parameters of the Foxhound

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.L. Wolfle	Assistant, Head, CU	VRB DRS
	E.J. Baas	Head, CU	VRB DRS
	F.J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15	1.05	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Accurate characterization of the foxhound is essential to development and definition of quality control programs for this laboratory animal. Blood pressure, growth rate, physiological and behavioral adaptation to environmental stress, birth weight, and prediction of neonatal survivability are among the areas studied. Outdoor paddock housing constitutes one major environmental variable. Uniformity among animals, within and between studies, significantly enhances validity of research results and reduces costs by eliminating unsuitable animals and decreasing the need for repetition of studies.

PHS-6040
(Rev. 10-76)

Objective: The objective is to accurately characterize the foxhound as a model for biomedical research.

Methods Employed: Longitudinal studies of reproduction, growth, bahavior, and disease processes are made. Blood pressure, viral and bacterial titers, and hematological studies identify mormal values and environmental characteristics that alter the normal or existing state. Data automation in the fall of 1979 will greatly extend this capability.

Major Findings: Basic reproduction, growth, hematalogic, and behavioral parameters have been identified. The colony serves as a standard for English and American foxhounds.

Significance: The foxhound is becoming prominent as a research animal. It is essential to determine normal physiologic and behavioral values to provide high-quality dogs for research. Identification of abnormal environmental parameters provide evidence of stress effects which impact adversely on many research projects. This ensures more uniform research results and increases efficiency by decreasing the need for duplication and eliminating unusable animals.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00036-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Mouse Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
OTHER:	K. P. Smith	Geneticist	CPS VRB DRS
	J. S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Bio Lab Tech	CPS VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal model of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: To identify and locate on the chromosomes of the laboratory mouse inherited traits which can be used in a wide range of biomedical research.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: Forty-five inbred strains and substrains of laboratory mice have been characterized for 31 inherited traits. These genetic markers are distributed on 13 of the 19 autosomal chromosomes.

Significance: The genetic profile will make it possible to monitor inbred mice for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use in the biomedical community. The genetic information obtained will also make these strains more useful as animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00037-02 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Fetal Surgery in the Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Expert Consultant, VMSS	VRB DRS
	J. D. Bacher	Chief, SU, VMSS	VRB DRS

COOPERATING UNITS (if any)
Comparative Medicine Unit, VMSS
Primate Research Unit, VMSS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.2	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Multiple uterotomies on pregnant rhesus monkeys are being done to expose the carpus or fetuses ranging in age from 120 to 163 days of gestation. The surgical procedure is being performed to establish an atlas for estimating skeletal age of the rhesus monkey before birth.

PHS-6040
(Rev. 10-76)

Objective: The aim of this project is to describe the surgical procedure used and to evaluate the effect of multiple uterotomies on pregant rhesus monkeys.

Methods Employed: Multiple uterotomies were performed in sixty timed-pregnant monkeys on alternate weeks starting at 120 or 127 days of gestation to expose the carpus of the fetal monkey. Anesthetic techniques, postoperative care, and the effect of an antiabortive medication (Vasodilan) were evaluated in this group of females.

Major Findings: While monkeys are anatomically similar to man, they abort more frequently, particularly after intrauterine surgery. At the beginning of the study, a relatively high incidence of aboration led to improvement of the standard surgical procedures and postoperative care. Oxygen flow rates were increased from one to two liters per minute, the use of heating lamps was prolonged (minimum 48 hours postoperative),and the administration of antiabortive medication (Vasodilan 10 mg) became standard postoperative procedure.

Significance: Current antenatal surgical procedures (in man) are presently used chiefly for diagnostics. Those used most frequently are amniocentesis, amniography, fetography, fetal skin biopsy, and fetal blood transfusions. Fetal and maternal risks are high in antenatal surgery and further improvement of techniques is needed.

Proposed Course:

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00038-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Linkage Analysis in the Laboratory Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	C. T. Hansen	Geneticist	SAS VRB DRS
	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS

COOPERATING UNITS (if any)
Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a chromosome map for the laboratory rat. The project is designed to identify inherited characteristics of the laboratory rat which can be used in a wide range of biochemical research. The primary areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) development of the chromosome map by standard genetic analysis; and (3) application of the revealed knowledge of the genetic characteristics to the exploration of new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: The primary objective is to identify inherited characteristics of the laboratory rat. The genetically variable traits will be used to develop a chromosome map and a genetic profile of the laboratory rat.

Methods Employed: The primary methods of analysis are: (1) isozymes by starch-gel electrophoresis; (2) complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and (3) cell surface alloantigens by cytotoxic methods.

Major Findings: A new polymorphism was found for peptidase and the strain profiles were determined for all 26 inbred strains. Special matings were set up for the production of F_1 hybrids and backcrosses for the genetic analysis of the linkage data. The isozyme pattern for the F_1 hybrid exhibited the expected F_1 phenotypic pattern.

Significance: The development of a chromosome map is much like putting together a jigsaw puzzle, the more traits which are already mapped the easier it is to map other traits. The linkage information from the backcross data presently being collected will make it possible to locate peptidase on the chromosme map. Once the location is determined it will make it easier to map other traits. Traits for which the genetic linkage is determined may also be used in the development of congenic strains.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00039-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Genetic Profile of the NIH Inbred Laboratory Rat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	C. T. Hansen	Geneticist	SAS VRB DRS
	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS

COOPERATING UNITS (if any)

Small Animal Section; VRB; DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a genetic profile for the laboratory rat. The project is designed to identify inherited characteristics of the laboratory rat which can be used in a wide range of biochemical research. The primary areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) development of the chromosome map by standard genetic analysis; and (3) application of the revealed knowledge of the genetic characteristics to the exploration of new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: The primary objective is to identify inherited characteristics of the laboratory rat. The genetically variable traits will be used to develop a chromosome map and a genetic profile of the laboratory rat.

Methods Employed: The primary methods of analysis are: (1) isozymes by starch-gel electrophoresis; (2) complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and (3) cell surface alloantigens by cytotoxic methods.

Major Findings: Twenty-six inbred strains and substrains have been characterized for ten inherited traits. A new polymorphism was found for peptidase and the strain profiles were determined. Strain profiles were obtained for three other traits which showed genetic variation. Genetic variation was not found among the remaining six traits which were analyzed.

Significance: The genetic profiles will make it possible to monitor the inbred rat strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use throughout the biomedical community. The genetic information obtained will also make these strains more useful animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00040-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Genetic Profile of the NIH Inbred Guinea Pig Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS
OTHER:	A. H. Grier	Biologist	CPS VRB DRS
	A. V. Williams	Bio Lab Tech	CPS VRB DRS

COOPERATING UNITS (if any)
Small Animal Section; VRB; DRS; and Frederick Cancer Research Center - NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory guinea pig inherited characteristics which can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biochemical and immunochemical techniques; (2) chromosome mapping by standard genetic analysis; and (3) application of the genetic characteristics to explore new animal models of pathogenesis.

PHS-6040
(Rev. 10-76)

Objectives: To identify and locate on the chromosomes of the laboratory guinea pig inherited traits which can be used in a wide range of biomedical research.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: Strain 2 and strain 13 inbred guinea pigs can be differentiated by three genetic markers: tissue hexose phosphatase, erythrocyte catalase, and an alpha-globular serum protein.

Significance: The genetic profile will make it possible to monitor the inbred guinea pig strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured due to their universal use in the biomedical community. The genetic information obtained will also make these strains more useful as animal models to the biomedical community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00041-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Cytogenetics of Laboratory Rodents

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. E. Breach	Cytogeneticist	CPS VRB DRS
OTHER:	H. A. Hoffman	Chief, Genetics Unit	CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to characterize the chromosome banding of the major animal strains used in biomedical research. To incorporate chromosome identification with somatic cell hybridization to identify new linkage relationships which cannot be obtained by standard genetic analysis.

Objectives: The introduction of cytogenetics into the NIH genetic monitoring program.

Methods Employed: Standard techniques of chromosome banding.

Major Findings: The establishment of laboratory protocols for chromosome identification from murine splenic lymphocytes and murine tissue culture cells.

Significance: Identify specific chromosome sets from interspecific hybrids and assign linkage groups to new genetic markers.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00042-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Development of a Standard Strain of Mice for Pertussis Vaccine Bioassays

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	C. T. Hansen	Geneticist	SAS VRB DRS
	C. R. Manclark	Research Microbiologist	PB BOB FDA

COOPERATING UNITS (if any)
Pertussis Branch; Bureau of Biologics; FDA

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a standard strain of mice to be used for pertussis vaccine bioassays. Two lines of mice have been selectively bred for their susceptibility and resistance to sensitization by the histamine sensitizing factor (HSF) of Bordetella pertussis and have been designated HSFS/N and HSFR/N. After 20 generations of selection, the ability to be sensitized by HSF in the HSFS/N line has increased to 70 percent, and in the HSFR has decreased to 0.5 percent. The two lines have been further characterized for 12 biochemical isozymes.

PHS-6040
(Rev. 10-76)

Objectives: The ideal animal model for biological assays would be a strain for which the dose-response relationship is accurately predictable within a given dose range. The objective of this project is to develop a strain of mice with predictable and stable characteristics for the control testing of pertussis vaccine and other biologics.

Methods Employed: From a base population of NIH Swiss Webster stock N:NIH (SW), two lines of mice were selectively bred for their susceptibility and resistance to sensitization by the histamine sensitizing factor (HSF) of Bordetella pertussis and were designated HSFS/N and HSFR/N respectively. Weanling mice were injected with a saline suspension containing one opacity unit of pertussis vaccine, after five days the mice were challenged with histamine diphosphate. A minimum of 12 offspring were tested in each generation from each breeding pair. Almost all deaths due to sensitization occurred within one hour of injection.

Major Findings: After 20 generations of selection, the ability to be sensitized to HSF in the HSFS/N line has increased from 31 percent in the base generation to 70 percent in generation 20, and in the HSFR/N line has decreased from 31 percent to 0.5 percent. The estimates of the realized heritability were 32 percent in the HSFS/N line and 22 percent in the HSFR/N line. The genetic profiles have been determined for both lines for 12 biochemical isozymes. There were phenotypic differences between the lines for two of the 12 loci tested.

Significance: The mice from HSFS/N strain provide the biomedical research community with an animal model which is highly sensitive to the lethal effects of histamine and is easily immunized by pertussis vaccine. The genetic profiles for the HSFS/N and HSFR/N strains indicate that each is isogenic and the profiles can be used in the future to uniquely differentiate these strains from all other strains in case of possible future genetic contamination.

Proposed Course: Continuation. Manuscript in progress.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00043-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Micromethods for Cytotoxicity Testing in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Crowell, Jr. Staff Fellow CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop techniques for rapidly typing the cell surface antigens expressed on lymphocytes from various strains of mice. A variety of methods using both vital dye exclusion and radioisotope release are being explored.

PHS-6040
(Rev. 10-76)

Objective: To develop a rapid, efficient, and accurate method for typing mouse lymphocytes.

Methods Employed: Several standard serological methods have been examined for their applicability to the routine needs of the genetic monitoring program.

Major Findings: Modification of the standard human leukocyte testing (HL-A testing) methods appears to meet most of the requirements for this project.

Significance: Successful completion of this project will permit the Genetic Monitoring Program to test a large number of mice for inheritable traits with a minimum expenditure of time and funds. Interest in this project has been expressed by a number of other laboratories concerned with quality control in large mouse colonies.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00044-01 VR

PERIOD COVERED
October 1, 1979 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Premature birth and postnatal development of Macaca mulatta: a comparison of growth factors

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: M. Michejda Comparative Anatomist, VMSS VRB DRS

COOPERATING UNITS (if any)
Veterinary Resources Branch

LAB/BRANCH
Veterinary Resources Branch

SECTION

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	1.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The bone maturation and physical growth of prematurely born Macaca mulatta are studied from birth to 24 months of age. A group of 12 prematurely born (range 140-150 days of gestation) monkeys of both sexes is observed. The growth parameters such as bone maturation (skeletal age), body weight, "dental age," cranial dimension, sitting height, length of upper and lower extremities are measured and compared with the data obtained from full-term animals. A correlation between appendicular bone maturation and gestational age is being established.

PHS-6040
(Rev. 10-76)

Objectives: The purpose of our study is to contribute to a better understanding of various problems related to growth and development of premature as well as neonatal Macaca mulatta. In particular, to observe the effects of intrauterine surgery on the physical development of newborn monkeys, to study the stages of bone maturation, the possibility of arrested growth and "catch up" growth phenomena. Finally to seek any correlation between gestational age and skeletal age.

Methods Employed: The standard anthropometric techniques are applied in the measurement of skull, extremities, and body dimensions. The radiographic techniques are applied to assess the skeletal age and status of bone maturation of prematurely born animals. Our longitudinal observations, based on measurements repeated every two weeks, continue until two years of age of each monkey. Longitudinal, quantitative assessment, and scoring of the ossification centers of the hand and wrist in our population are compared with growth standards and age indicators of full-term animals. The measurements are compared using the Student "t" test method.

Major Finding: Significant correlation (P 0.005) between skeletal age and gestational age was found. No ill effects of fetal surgery on the normal course of physical growth were observed.

Significance: This study should provide more important information on growth and development of neonate M. mulatta. Moreover, it should contribute to better understanding or various prenatal stresses on the skeletal development of the infant monkey.

Proposed Course: Project completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00045-01 VR

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Flexible Fiberoptic Bronchoscopy of the Rhesus Monkey (Macaca mulatta)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Ira J. Strumpf	Senior Staff Fellow	PB NHLBI
	John D. Bacher	Chief, SU, VMSS	VRB DRS
	James E. Gadek	Senior Investigator	PB NHLBI
	Martin L. Morin	Chief, PRU, VMSS	VRB DRS

COOPERATING UNITS (if any)

Surgery Unit, VMSS
Primate Research Unit, VMSS

LAB/BRANCH

Veterinary Resources Branch

SECTION

Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.3	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to develop an animal model for human emphysema. Under direct visualization through the bronchoscope, foreign or natural materials such as $C5_a$ or endotoxin will be installed into right lung.

The left lung will serve as a control. Weekly saline lavages for six weeks will be assayed for neutral proteinases, elastase, and alphal antitrypsin activity as determinates for the development of emphysema.

PHS-6040
(Rev. 10-76)

Objective: The aim is to produce a valid animal model for the study of human emphysema.

Methods Employed: A pediatric fiberoptic bronchoscope (O.D. 4.5 mm; length 605 mm) or an adult bronchoscope (O.D. 5.8 mm, length 605 mm) were used for inspection, saline lavages, and photography. After installation of various substances into the right lung, saline lavages using the adult bronchoscope are being done to determine if emphysema is developing.

Major Findings: The project is in the development stage.

Significance: The etiology of emphysema is still unknown. A good animal model is needed to effectively study this disease process.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00046-01 VR

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Evaluation of Donor Safety in Leukopherisis of Canines

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.J. Baas	Chief, CU, ACS	VRB DRS
Other:	F.J. Judge	Chief, ACS	VRB DRS
	J.E. French	Research Physiologist	DBBP BoB
	J.C. Fratatoni	Director, BP	DBBP BoB

COOPERATING UNITS (if any)

Blood Products Branch, Division of Blod and Blood Products
Bureau of Biologics, FDA

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Leukopheresis on canine blood donor dogs is being conducted to determine if repeated removal of lymphocytes affects the immune response. Information obtained on the maximum frequency or total number of leukopheresis donations is to be extrapolated for human donors.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if frequent removal of lymphocytes will deplete their number or have a detrimental effect on the immune process.

Methods Employed: Foxhound blood donor dogs are being leukopheresised with a Haemonetics Model 30 Blood Processor using techniques for human donors. The lymphocytes are being separated and stimulated with mitogens to measure their ability to respond.

Significance: There is a definite trend to regular and frequent granulocyte donations in human medicine. The effects on specific immune responses of the long-lived T lymphocyte are poorly misunderstood. This study with the dog model will determine if there are definite detrimental effects from frequent donation.

Proposed Course: The preliminary project is in progress. If the present methods prove effective in dogs, this project will serve as a basis for more comprehensive studies in humans and the canine mode.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00047-01 VR

PERIOD COVERED
October 1, 1978 - September 30, 1979

TITLE OF PROJECT (80 characters or less)

Screening Laboratory Animal Diets for Chemical Contaminants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.J.KNAPKA Nutritionist, SAS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
Division of Research Services, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.01	.24

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A program has been established for the routine analyses of feed samples for chlorinated hydrocarbons, polychlorinated biphenyls, organo-phosphates, lead, arsenic, cadmium, mercury, nitrate and aflatoxins. Nitrosamines assays are being conducted on feed samples selected at random. The objective of this program is to document the concentrations of these potential contaminants in natural ingredient laboratory animal diets and to establish the maximum concentrations that can be attained on a practical basis.

PHS-6040
(Rev. 10-76)

Project Descriptions:

Objectives: To collect data regarding the concentrations of potential chemical contaminants in laboratory animal diets in order to obtain a basis for establishing maximum acceptable concentrations of these contaminants in diets for laboratory animals.

Methods Employed: Manufacturers of all NIH laboratory animal diets are required to collect representative samples of each production batch of diet. These samples are mailed to an independent laboratory where they are analyzed for chlorinated hydrocarbons, polychlorinated biphenyls, organo-phosphates, lead, arsenic, cadmium, mercury, nitrate and aflatoxins under an NIH contract. In addition, diet samples are collected on a random basis in the NIH warehouse and mailed to a university laboratory for nitrosamines analysis. All assay results are mailed directly to the appropriate NIH personnel for evaluation.

Major Findings: None to date

Significance: In recent years various NIH investigators have expressed concern regarding the potential effect residual concentrations of dietary chemicals can have on animals involved in various kinds of research. A major issue in this regard is lack of knowledge concerning the biological effect of low concentrations of dietary chemical contaminants. This program is designed to document dietary contaminant levels so these data are available for the evaluation of experimental data.

Proposed Course: Continuation.

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Karamian, N. A.: High Purity, Bacteria-Free Endotoxin-Free Water, *NIH Research Advances,* DHEW Publication No. (NIH) 78-3, pp. 86.

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